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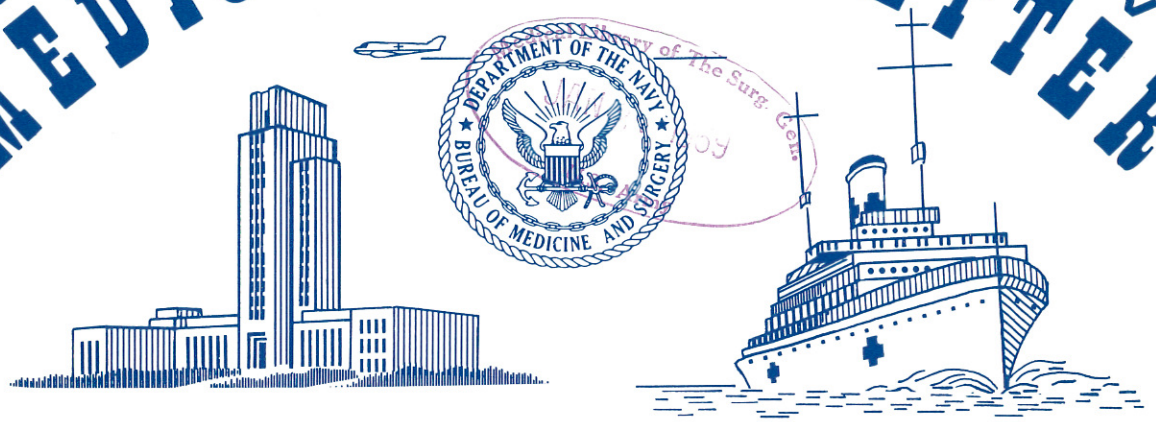
UNITED STATES NAVY MEDICAL NEWS LETTER



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Policy

The U.S. Navy Medical News Letter is basically an official Medical Department publication inviting the attention of officers of the Medical Department of the Regular Navy and Naval Reserve to timely up-to-date items of official and professional interest relative to medicine, dentistry, and allied sciences. The amount of information used is only that necessary to inform adequately officers of the Medical Department of the existence and source of such information. The items used are neither intended to be, nor are they, susceptible to use by any officer as a substitute for any item or article, in its original form. All readers of the News Letter are urged to obtain the original of those items of particular interest to the individual.

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Please forward changes of address for the News Letter to Editor: Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 20390 (Code 18), giving full name, rank, corps, old and new addresses, and zip code.

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SUDDEN UNEXPECTED DEATH IN INFANCY SYNDROME

Edward B. Shaw, MD, San Francisco, Amer J Dis Child 116(2):115–119, August 1968.

Nasal obstruction due to mild infection may well be the trigger for apnea and asphyxia in the sudden death (SUD) syndrome in infancy. This hypothesis is based on the well known reluctance of infants to breathe through their mouths. Choanal atresia is a recognized cause of neonatal death. Some babies appear to be almost completely unable to adopt oral respiration and this sometimes persists up to 5 or 6 months of age. These unexpected deaths almost alway occur at night, when the infant is unobserved and asleep. The postmortem evidence of infection can account for a collection of nasal secretion.

The records of 28 infants (among 19,000 live births), who died with the SUD syndrome and who had carefully recorded "well baby visits" were reviewed. The findings failed to indicate any physical or immunological defect, allergy, or injury sufficient to account for this terminal event. All deaths occurred at less than 6 months of age.

The death of infants without evident illness beyond slight upper respiratory infection and for whom no adequate cause of death is found at autopsy is now appropriately referred to as sudden unexpected death (SUD). These babies are usually found dead in bed; this is often called "crib death" or "cot death," although not all die in bed.

Autopsy findings reveal evidence of respiratory failure and asphyxia, usually with pulmonary edema and hemorrhages on the surface of the thymus, pericardium, pleura, and elsewhere in the thorax. Almost invariably some signs of infection are detectable in the lungs and upper air passages, but these are of insufficient magnitude to account for death. Most coroners list these deaths as due to interstitial pneumonitis because of the evidence of minimal respiratory infection and the failure to detect anything else of significance; sometimes they add "death from unknown cause."

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These fatalities are not uncommon in the United States and Canada; reportedly they occur in 2.5 to 3/1,000 live births, amounting to more than 15,000 deaths annually, although this total figure probably includes many sudden deaths from causes in which actual illness is simply not well established. The present study was pursued to discover the occurrence of this syndrome in carefully supervised follow-up care of infants during the first year of life with the hope that a hypothesis concerning the etiology of SUD might thereby find support.

The Study

It is manifestly impossible to design a purely prospective study of this problem, but an approach was afforded by utilization of the records of Kaiser Foundation Hospital of Oakland, Calif. This prepaid medical facility serves a representative sample of the general population; prepayment for care excludes many of the well-to-do as well as the underprivileged, thus differing from the usual clinic population. All children born in this hospital, whose parents consent, are enrolled in an on-going study at the Child Health and Development Center of the University of California School of Public Health. Entire families are included and records of both parents and children are available for the study of family history and for the course of pregnancy and delivery. Under the Kaiser plan, all infants have careful examination at birth and on discharge from the nursery, and receive continuing well-baby care for supervision and immunization. Because of the prepaid care feature and the constant availability of outpatient facilities and emergency room, infants are brought in for even minor complaints, so that it is unlikely that any significant illness occurs without examination of the infant by a physician.

From Jan 1, 1960, through Dec 31, 1967, there were 19,439 live births in this hospital. Among these there were 409 deaths recorded from all causes; at least 40 of these were sudden death. By strict limitation of the definition of SUD described previously, 28 of the 40 could be so classified.

These figures do not establish the exact incidence of the syndrome. Some patients were lost to follow-

up; some deaths occurred elsewhere, and in some patients data were inadequate. The attempt was made simply to detect those who were classical examples of this syndrome. Excluded were those with very definite causes for sudden death: anomalies, congenital heart disease, fulminant infection, injury, etc. Two siblings died suddenly, one aged 2 years, the other, 15 months; both showed minimal postmortem findings, but the 2-year-old died less than one hour after a mild head injury and his brother was found dead following a two-hour nap beside his mother. These two in one family were thought to represent other than classical SUD.

These patients consisted of 20 boys and eight girls (the usually reported sex distribution) and included 21 white infants, six Negro infants, and one Mexican infant (consistent with the proportion in the hospital population). Birth dates were distributed randomly throughout the year. The average birth weight was 2.95 kg (6½ lb); only two patients weighed under 2,500 gm (5½ lb), one of whom was a surviving twin. All infants were products of normal pregnancy and delivery, followed normal periods of gestation, were normal on examination in the nursery, and were free from neonatal complications. During follow-up outpatient care, eight of these children had mild respiratory infections sometime prior to SUD; two of them were treated with antibiotics for 24 hours. Prior to the time of death, none had shown any evidence of especial vulnerability to infection.

The average age at which death occurred was 2.8 months (range 2 weeks to 6 months); 19 infants died between 2 and 4 months, and one was over 6 months of age. Deaths occurred during every month of the year, more frequently during the months of greatest incidence of respiratory infection: 19 deaths during October through March, and 9 deaths in April through September. This distribution did not suggest significant correlation with the epidemic peak of any specific viral disease.

Each of these deaths was investigated by a coroner's pathologist. The autopsy surgeon ascribed death in 26 infants to interstitial pneumonitis, often with accompanying pulmonary edema; one death was attributed to "peribronchitis," which may have been the same thing; and one death was attributed to suffocation, which may have been based only on suspicion. One infant with interstitial pneumonitis was said to have "necrotizing laryngitis." In still another case, lymphocytic and plasma cell infiltration of the lung parenchyma was present, and in one infant, milk had been aspirated into the bronchi. Detailed virologic and bacteriologic studies were not available.

These were definitely deaths from respiratory failure and asphyxia, with some evidence of pulmonary and respiratory tract infection which was, however, invariably much less than that which would satisfactorily account for death. The event was completely unexpected and usually occurred at night while the baby was unattended. No one saw these babies die, and usually death had occurred several hours before it was discovered.

Comment

Retrospective studies by many pathologists have completely failed to establish a single cause for this syndrome and no infectious agent has been common to a significant number of victims. The autopsy findings in the present series corresponded in almost every way with previous studies and similarly excluded gross abnormality of heart, lung, and brain.

Previous Hypotheses.—An excellent review of this baffling subject by Valdes-Dapena in January 1967, accompanied by an extensive bibliography, enumerates most of the theories proposed up to that time. New hypotheses continue to be added at a furious rate, but are in large part speculative and unproven. We may consider the present series of 28 cases in the light of some of these theories. Admittedly the number is small.

1. *Status thymolymphaticus* represents a concept which for many years was believed to be the cause of this disaster; the concept has now been completely rejected. Infants who die quickly have a larger thymus than those who die following more prolonged infection. None of the infants in this series showed significant thymic enlargement.

2. *Suffocation by bed clothing or harnesses* which restricts activity was held responsible long ago, but evidence of this could scarcely avoid detection by an alert pathologist. Wooley demonstrated that suffocation by bedding could occur only with completely impervious rubber or plastic material. This was suspected, probably erroneously, in only one of our infants.

3. *Fulminant infection* has often been assumed as a cause. However, infection of such overwhelming virulence would be expected to provide more evidence for the pathologist than any of these cases revealed, and the many reported studies would be expected to disclose some common infectious agent. Pneumocystis carinii pneumonia has not been completely excluded in these deaths, but evidence of this infection should have appeared earlier in life and should have been indicated by postmortem findings.

4. *Milk allergy* (anaphylactic hypersensitivity, regurgitation of cows' milk, aspiration into the lungs, and anaphylactic death) has also been advanced as a cause. Antibodies against milk are commonly present in infants, children, and adults without relationship to symptomatology. Anaphylactic death should be expected to cause characteristic postmortem findings in the lungs; none were found in this or any other series. If these infants were highly sensitized to milk, they should have had eczema or have shown other prior evidence of milk intolerance. Only two of the infants in this series had any eczematous lesions, and these were observed at only one visit and were not severe.

5. If these infants were suspected of being *immunologically defective,* ie, with hypogammaglobulinemia, Wiskott-Aldrich syndrome, etc, they should have had a history of repeated infections, or poor response to therapy, but not a sudden lethal response to a single simple infection. None of the infants in this series had such a history of repeated infection.

6. *Extreme edema of the larynx and trachea* has been hypothesized as due to some unknown etiology, but this would hardly have been so transient as to escape detection at postmortem examination. However, sudden extreme laryngospasm (the "false croup" of an earlier generation) might not show persistent postmortem evidence. Laryngospasm with sudden respiratory arrest and death from asphyxia is consistent with most of the findings, although the primary cause of laryngospasm remains conjectural.

7. *Hemorrhage* into the cervical cord from some unsuspected trauma has been proposed as a cause of neurogenic respiratory arrest. These hemorrhages, described in seven of eight infants, may have been traumatic but may simply have been due to terminal asphyxia. These findings have escaped prior detection and have not been confirmed.

8. A recently quoted theory (apparently unreported in medical literature) is that these babies are *smothered by a mother with postpartum psychosis* who seizes the opportunity late at night for murder. This is a cruel explanation which could only accentuate the guilt feelings of parents who commonly feel responsible for these deaths anyhow. Coroners are most alert to the possibility of the "battered child syndrome" and evidence of trauma, and they would almost always detect evidence to support such a hypothesis.

9. Geertinger has proposed that *"subvalidity of the parathyroids"* may be responsible because there are (1) significant seasonal relationships to the time of birth; (2) anomalies of the parathyroids and thymus; (3) alteration in calcium levels; and (4) preponderance in the male sex. This hypothesis has not been confirmed and was rejected by Valdes-Dapena.

Speculation

The reported facts concerning these cases of SUD seemingly demand a simple explanation in which respiratory obstruction might be triggered by a relatively minor cause. The following are considerations in formulating a hypothesis to explain the events.

1. These infants commonly show some evidence of respiratory infection, usually minor but sufficient to justify an autopsy diagnosis of interstitial pneumonitis with death due to respiratory failure and asphyxia.

2. Newborn infants almost obligatorily breathe through the nose. If the nares of the newborn are gently occluded, only a few babies promptly resort to mouth breathing. Others struggle violently to effect nasal respiration and finally become distressed, angry, cry, gasp, and then adopt some degree of successful oral breathing. Still others continue to attempt to establish nasal breathing by violent and ineffective efforts of accessory muscles of respiration, with apparently some laryngospasm. This can be demonstrated in the sleeping infant by gentle occlusion of the nares (rather than by pinching the nose, which causes the infant to cry and gasp). How long respiratory arrest will continue cannot be determined except by prolonged and inappropriate experimentation. In most infants mouth breathing seems to be a purely voluntary effort and not simply a reflex in response to nasal obstruction. Not all infants respond in this way, but up to 6 months of age some of them seem almost incapable of oral respiration.

3. It is well recognized that choanal atresia in the neonate may cause death from asphyxia if not promptly discovered and relieved. This anomaly has been proposed as a cause of SUD, but its presence is unsupported by pathologic findings. It is worth noting that if operation for atresia is deferred, it is necessary to place an airway in the mouth secured by a tape around the neck to assure mouth breathing and prevent death from asphyxia. This further substantiates the obligatory nature of nasal respiration in many infants and the difficulties which attend nasal obstruction.

4. Some infants with only upper respiratory infection and profuse nasal discharge may be observed

to have marked dyspnea, cyanosis, and hyperpnea which can be relieved by nasal aspiration.

5. The experimental studies of Handforth in rats indicate that temporary respiratory obstruction results in fatal apnea with pathology resembling that in the SUD syndrome.

Proposed Hypothesis.—It is proposed that the trigger mechanism which induces respiratory arrest and asphyxia occurs in unconscious, sleeping, and unattended infants with nasal obstruction due to infection and who belong to a group of those incapable of voluntarily initiating oral respiration. Nasal obstruction may be the sole factor which provokes respiratory failure. Spasm of accessory muscles of respiration and spasm of the larynx sufficient to cause asphyxia and death ensue.

This hypothesis is consistent with the fact that these deaths occur during sleep, usually at night, when the infants are unobserved and when there is mild evidence of respiratory infection. Although the hypothesis must remain a conjecture, it appears more persuasive than the many hypotheses previously proposed and is consistent with the idea that some very simple mechanism is involved. It can certainly be most persuasively supported by gently occluding the nostrils of small infants, which will illustrate how violently some will struggle against mouth breathing. Common colds and other upper respiratory symptoms are not extremely frequent in infants under 6 months of age, but those with significant nasal discharge may be safeguarded against these inexplicable tragedies by frequent changes of position, induced cough or cry, and the use of nasal aspiration. At all events, these infants should not be kept at a distance from watchful parents.

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(The figures and references may be seen in the original article.)

RAYNAUD'S PHENOMENON AS LEADING SIGN IN LUPUS ERYTHEMATOSUS—REPORT OF THREE CASES AND CLASSIFICATION OF CRYOPATHIES*

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Cryopathies; Raynaud's phenomenon; systemic lupus erythematosus

Raynaud's phenomenon has been recognized as an important complication of systemic lupus erythematosus (SLE). As such, it provides a diagnostic clue to the nature of the underlying disease in patients with otherwise atypical or not fully developed manifestations of SLE.

It is the purpose of this presentation to report three female patients in whom the diagnosis of SLE was established only as a result of diagnostic workup for Raynaud's phenomenon, and two of whom responded favorably to corticosteroid therapy. In all three patients, manifestations of vascular pathology preceded the onset of Raynaud's phenomenon. To facilitate the differential diagnosis of Raynaud's phenomenon, a classification of cold hypersensitivity states, or cryopathies, is presented.

Case Reports

Case 1

J. M., a 29-year-old Latin American female, was well until two months following the sixth pregnancy in February, 1966. At this time, she experienced the first of four episodes of thrombophlebitis in the left calf, each of which was treated with injections of corticosteroids. In June, 1966, on exposure to cold or when under emotional stress, she noted blanching and numbness of the fingers, progressing to cyano-

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sis and pain. She also experienced pain in the ear lobes and nose on exposure to cold. There was no family history of a similar disorder.

On admission, the patient's blood pressure was 122/82 mm Hg, pulse rate was 88/min, respirations were 19/min; and the rectal temperature was 102F. The funduscopic examination revealed no abnormalities. Two enlarged lymph nodes (1.5 cm x 2.0 cm) were palpated in the right posterior cervical area. The lungs were clear and no cardiac murmurs were heard. There was no palpable hepatosplenomegaly. The tip of the right fifth finger exhibited a 1 cm x 1 cm depressed, black area of necrosis, and Raynaud's phenomenon could be easily elicited in the fingers of both hands. All pulses were full and equal and the neurological examination was normal.

Erythrocyte count was 5.3 x 10^6/mm^3, the hemoglobin was 13.9 g%, and the total white blood count was 5,300/mm^3 with a differential of 52 percent neutrophils, 5 percent banded neutrophils, 13 percent eosinophils, 1 percent basophils, 22 percent mature lymphocytes, 5 percent atypical lymphocytes and 2 percent monocytes. Bone marrow examination showed a moderate increase in mature plasma cells, reticulum cells and lymphocytes.

The urinalysis was normal. Several blood and urine cultures were negative and the sputum culture revealed a normal flora. In the stool, the following parasites were found: *Endamoeba histolytica, Endamoeba coli, Endamoeba Hartmani, Blastocystis Hominus* and *Endamoeba Nana.* Total serum proteins were 7.9 g% and serum paper electrophoresis revealed slight hypoalbuminemia (3.4 g%) and polyclonal gammopathy (γ-globulin—2.8 g%). The results of the cryopathy studies are presented in Table 1.

Skin and muscle biopsy from the calf revealed signs of arteritis without fibrinoid necrosis. Cervical lymph node biopsy showed reactive hyperplasia. Renal biopsy specimens showed focal hyaline fibrinoid thickening of scattered glomerular tufts with few polymorphonuclear neutrophils. There was patchy fibrinoid necrosis of the arterioles and the glomeruli were essentially normal.

During the early part of the patient's hospital stay, the finger tip healed spontaneously. The temperature rose to 104F and she developed transient blindness in the left eye. The patient was given 60 mg of prednisone daily. Within 24 hours the temperature returned to normal, visual acuity was restored, and the number and severity of episodes of Raynaud's phenomenon decreased. Prednisone was reduced to 30 mg daily; Raynaud's phenomenon recurred, however, necessitating the prednisone dosage to be increased to 45 mg per day. Subsequently, the dose was reduced slowly. In August, 1967, the patient was last seen in the clinic. At that time, she was taking 10 mg of prednisone daily. She reported that she was feeling well and no longer experienced Raynaud's phenomenon.

Case 2

S. R., a 20-year-old white female, was admitted for the third time on December 14, 1963, with a chief complaint of convulsions which had occurred only that morning. The patient had had diabetes mellitus since age 12. She was first hospitalized at age 16 with an adolescent adjustment reaction. Physical examination at that admission was normal except for obesity. Results of routine laboratory tests were normal. The patient was not seen again until age 18 when she was admitted with complaints of weak-

TABLE 1.—*Summary chart of pertinent clinical and laboratory data*

Clinical and laboratory manifestations	Case 1 29-year-old Latin American female	Case 2 20-year-old Caucasian female	Case 3 23-year-old Latin American female
First vascular symptoms	Thrombophlebitis	Cerebral vascular involvement	Pulmonary embolus(?)
Time from disease onset to development of Raynaud's phenomenon	2 months	2 years	20 months
LE tests			
Latex tests (Hyland)	Positive	Positive	.....
Cell tests	Tart cells but no classical LE cells	.....	Positive
RA latex test (Hyland)	Negative	Negative	Positive
Cryofibrinogen	Normal	Normal	Normal
Cryoglobulins	Negative	Negative	Negative
Cold agglutinins	Negative	.....	Positive (1:512)
Biologic false tests for syphilis	No	Yes	Yes

ness and slurred speech for the previous five days. She was withdrawn, uncooperative and somnolent. The left arm and hand were minimally weak and she was almost totally aphasic. The right seventh cranial nerve was weak; there was no papilledema or opisthotonus. The deep tendon reflexes were hyperreactive, especially on the right side and Babinski and Hoffman's reflexes were present bilaterally. The Romberg's test was positive and she had an atactic gait. A left cerebral arteriogram showed no filling of the posterior branches of the middle cerebral artery and decreased opacification of the anterior cerebral artery. The blood count was normal. Urinalysis revealed a 2+ reaction for proteins. Total serum proteins were 6.8 g%. The direct Coomb's test, RA latex and several LE precipitin and gel tests were negative. The serum VDRL and the Kolmer test were positive (1:44 dilution); whereas, the Reiter's protein complement fixation test, the fluorescent treponemal antibody test and the spinal fluid Kolmer test were negative. Speech improved gradually and motor weakness and ataxia subsided, but the reflexes remained hyperactive. One year prior to the last admission, the patient began experiencing extreme pain in both hands, associated with blanching and precipitated by exposure to cold. One week before admission she developed "darkening" of the finger tips. On the morning of admission she had a generalized convulsion. At this time, the blood pressure was 180/120 mm Hg, the pulse 120 beats/min, respirations were 25/min and the rectal temperature was 100.8F. Funduscopic examination showed no abnormality. There was no palpable organomegaly. The tips of the third and fourth fingers of the left hand and the tip of the right fifth finger were black and gangrenous. The patient was conscious but irrational. Deep tendon reflexes were hyperactive and bilateral Babinski reflexes were elicited. A right carotid arteriogram showed spasm of the intracerebral vessels. An electroencephalogram indicated a diffuse abnormality.

The hemoglobin was 8.9 g%; total white blood count was 13,700/mm^3 with 91 percent neutrophils, 7 percent lymphocytes and 2 percent monocytes. Urinalysis revealed sp. gr. 1.030, 4+ reaction for protein and glucose, 20-30 erythrocytes and 4-8 granular casts per high power field. Total serum proteins were 4.8 g%. Serum electrophoresis revealed marked hypoalbuminemia (1.2 g%) and a low normal γ-globulin fraction (0.8 g%). Results of cryopathy studies are presented in Table 1.

The patient developed spiking fever to 105F. All blood cultures were negative and sputum culture revealed a normal flora. The urine contained greater than 10^5 E. Coli/ml. Blood sugar levels were consistently above 600 mg%. Initially, these findings were interpreted to be indicative of septicemia and large doses of antibiotics were administered. Additionally, methylprednisolone and ACTH were given. The patient's condition deteriorated rapidly and she became unresponsive. The urine output decreased and the hemoglobin concentration fell to 6.5 g%. She died 12 days after admission. Histological examination of autopsy specimens revealed lesions of both diabetic glomerulosclerosis and lupus erythematosus. The latter was not the inflammatory type of lesion but more of a sclerosing type of change, i.e., a diffuse, nonhyaline lupus glomerulosclerosis.*

Case 3

E. R., a 23-year-old Latin American female was first hospitalized in December, 1959, complaining of pain in the finger tips of three weeks duration. She stated that she had been well until March, 1958, when she had a 10-day episode of migrating polyarthritis. In May, 1958, she again developed arthritis, primarily with shoulder and neck involvement. This was effectively treated with large doses of aspirin for 10 days. In April, 1959, the patient had a complete abortion without curettage. One week later, this patient developed chills, fever, dyspnea, chest pain, liver enlargement and ankle edema. She was admitted to the local hospital and given oxygen therapy, diuretics and possibly digitalis. Her symptoms cleared rapidly and she was discharged in one week. She did well until August, 1959, when she again began having pains in her fingers when exposed to rapid changes of temperature. By December, 1959, the patient's digits were constantly painful and necrosis developed. An LE cell test was positive and the patient was treated with dexamethasone, 0.75 mg every four hours.

On admission, the blood pressure was 130/80 mm Hg, the pulse rate was 92/min, respiration 16/min and the rectal temperature was 103F. The fingers were cold and pale with a mottled cyanosis of the distal phalanges. There was gangrene of the tip of the right ring finger. The lower extremities had a mottled appearance below the knees and they were cool to the touch. The right middle toe showed dry gangrene. Chest X-ray showed no abnormalities and the electrocardiogram revealed sinus tachycardia.

* We kindly acknowledge the interpretation by Dr. B. H. Spargo, Professor of Pathology, University of Chicago, Chicago, Illinois 60637.

Erythrocytes were 4.18 x 10^6/mm^3 and hemoglobin was 12.7 g%. Total white blood count was 15,000/mm^3 with 83 percent mature granulocytes, 5 percent metamyelocytes, 1 percent eosinophils, 5 percent lymphocytes, 2 percent atypical lymphocytes and 4 percent monocytes. Erythrocyte sedimentation rate was 33 mm/1 hr. Urinalysis revealed no abnormalities. Blood cultures were negative. The cryopathy studies are presented in Table 1. The Kahn test was positive, but the Kolmer test was negative. Total serum proteins were 9.0 g% and electrophoretic fractionation revealed hypoalbuminemia (3.1 g%) and polyclonal gammopathy (γ-globulin-4.1 g%).

The patient was treated initially with hydrocortisone i.v. which was gradually changed to a low dose of oral prednisone and 750 mg chloroquine daily. At various time intervals during the three months hospital stay, vasodilators and heparin were administered. After a stormy course, the pain in the hands gradually subsided. The cyanosis cleared and the gangrenous process was halted.

Discussion

Raynaud's phenomenon is a well-known complication of systemic lupus erythematosus, occurring with a frequency of 10-35 percent of patients with SLE. It may be the leading sign in patients with otherwise atypical and nondiagnostic manifestations of this disease. In each of the three patients described, the diagnosis of LE was established only after a systematic search for causes of cold hypersensitivity states, or cryopathy, was made. In each instance, a prolonged clinical course, marked by serious complications, especially of a vascular nature, was encountered before a diagnosis of SLE was made. Earlier recognition of SLE and treatment might have prevented or modified the deleterious clinical course of the second case, and probably would have benefited the other two patients.

The therapeutic response to corticosteroids in patients with SLE and Raynaud's phenomenon, is often satisfactory, although others have noted no definite benefit. In two of the patients presented, the institution of corticosteroids therapy was followed by definite improvement of the patient's general condition and the Raynaud's phenomenon. In the third patient, however, death occurred before treatment with corticosteroids became effective.

The diagnosis of SLE complicated by Raynaud's phenomenon may not be evident, at least initially, on routine examination. Thus, in none of the three patients presented was there clear-cut clinical or laboratory evidence of SLE. There was no evidence of pleurisy, pericarditis or photosensitivity. Leukopenia was present in none, and anemia, abnormal urinalysis and marked hyperglobulinemia in one patient, respectively. Only after a systematic evaluation of possible causes of cryopathy had been made, was the diagnosis of SLE established. The demonstration of positive LE cell tests and/or positive LE latex tests, positive tests for syphilis, considered to be biologically false tests, and histological evidence, supported the diagnosis of SLE in the patients under discussion. In all three patients, the occurrence of Raynaud's phenomenon was preceded by manifestations of vascular pathology (Table 1).

Table 2.—*Classification of cryopathies*

I. *Raynaud's disease.* Idiopathic, essential disorder, mainly affecting females during 2nd to 4th decades, without recognizable underlying disorders, upon long-term follow-up.

II. *Cryoproteinemias.* Occurrence of cold sensitive plasma proteins.
1. *Cryoglobulinemias.* Found in association with monoclonal (especially macroglobulinemia Waldenström) or polyclonal gammopathies (e.g., rheumatoid arthritis).
2. *Cryofibrinogenemia.* Rare.

III. *Paroxysmal cold hemoglobinurias.* Antibody-caused hemolysis upon exposure to cold.
1. *Cold agglutinin syndrome.* Due to increased cold agglutinins, usually of anti-I-γM-globulin-variety; either acute (e.g., PPLO infections) or chronic (related to macroglobulinemia Waldenström).
2. *Cold hemolysin syndrome.* Due to Donath-Landsteiner (i.e., anti-P+P_1) antibodies; either acute (Non-syphilitic) or chronic (syphilitic).

IV. *Collagen disorders.* These vasculogenic cryopathies include:
1. Scleroderma (commonly associated with Raynaud's phenomenon)
2. Lupus erythematosus
3. Dermatomyositis
4. Rheumatoid arthritis (including its variants)

V. *Occlusive arterial diseases.*
1. *Nonoccupational diseases,* such as arteriosclerosis obliterans and thrombangitis obliterans.
2. *Occupational diseases,* including vibration tool (pneumatic hammer, etc.) disease, Raynaud's phenomenon in typists, pianists, cashiers, etc.

VI. *Neurovascular compression syndromes* (i.e., shoulder-girdle compression, thoracic outlet syndromes).
1. Scalenicus anticus syndrome
2. Cervical rib syndrome
3. Hyperabduction syndrome
4. Costoclavicular syndrome

VII. *Miscellaneous disorders.*
1. Cold urticaria
2. Intoxications (e.g., ergotism)
3. Tumors (e.g., glomus tumors)
4. Angiokeratoma corporis diffusum (Fabry)
5. Paramyotonia congenita
6. Injuries to brain, spinal column, nerve roots or trunks.
7. Unexplained causes of Raynaud's phenomenon

Since Raynaud's phenomenon in SLE, at least in selected cases, appears to be amenable to vigorous treatment, early recognition of this cause of Raynaud's phenomenon is essential. The term cryopathy has been suggested for cold hypersensitivity states which can manifest themselves by a variety of clinical symptoms and signs and which are aggravated by exposure to cold. Precise differential diagnosis of cryopathies is a prerequisite for an effective therapeutic approach. For instance, results of sympathectomy are usually disappointing in patients with Raynaud's phenomenon associated with scleroderma or SLE, whereas, idiopathic Raynaud's disease often responds favorably. In order to facilitate such a differential diagnosis, a classification of cryopathies, modified from an earlier report, is presented (Table 2).

Summary and Conclusions

Three female patients are described with vascular abnormalities as premonitory, and Raynaud's phenomenon as leading sign of systemic lupus erythematosus. The diagnosis of SLE was established only during a systematic diagnostic workup for cryopathies.

The salutory therapeutic response of Raynaud's phenomenon to corticosteroids necessitates early recognition of SLE as the underlying disease. In patients with cryopathy of obscure etiology, a systematic differential diagnostic evaluation is required. A classification of cryopathies is presented as a guideline.

(The references may be seen in the original article.)

PERIPHERAL NEUROPATHY
CHANGING CONCEPTS, DIFFERENTIAL DIAGNOSIS AND CLASSIFICATION

Peter James Dyck, MD, Med Clin N Amer 52(4):895–908, July 1968.

By definition, peripheral neuropathy includes all diseases which affect peripheral nerve tissues—that is, the portions of the roots lying outside the pia-mater, and the dorsal root, and autonomic ganglia, plexuses and peripheral nerve fibers. Thus, all focal or generalized disorders of these structures could be accepted. While this anatomic distinction is simple, in practice it is difficult to know what disorders ought to be included, since many of them affect both central and peripheral nervous tissue. In anterior horn cell diseases, structural and functional alterations occur also in the peripheral nerves; and in dorsal ganglion cell disorders, degeneration of axons occurs both in peripheral nerves and in dorsal columns of the spinal cord. Furthermore, some disorders of neurons, some of whose cell bodies lie in the central nervous system, are first revealed by changes in the distal portions of their axons (the so-called dying-back phenomenon). Such patients may have the manifestations of peripheral nerve involvement only. By convention, focal disorders such as those caused by trauma, compression, and tumor are not usually included under this designation, and they will not be discussed here. Two reviews of them, however, are listed among the references.

Diagnostic Investigation

Obtaining the History. The spontaneous description by the patient will often indicate to the knowledgeable physician whether or not there is disease of peripheral nerves. Patients with neuropathy describe their symptoms by characteristic expressions—for instance, they use such words as asleep, bandlike, tightness, prickling, burning, searing, jabbing, sticking, coldness or rawness. These symptoms are usually localized in the extremities. A statement that some part is "numb" may not indicate disease of the nervous system, since the word is used loosely by patients and may mean lifeless, tired, weak, or uncomfortable. Many a person with aches and pains —especially if these are poorly localized—does not have neuropathy, and the designation of neuritis for this situation is incorrect. Patients with muscle weakness usually do not talk about weakness but about what they cannot do—fasten safety pins or buttons, turn a key in a lock, walk without stumbling, pick up their toes and climb stairs. The patient with neurasthenia often complains of weakness but may mean tiredness, listlessness, lack of initiative or depression.

Several lines of inquiry should be followed in every case of polyneuropathy. The patient should be asked about symptoms of such systemic diseases as carcinoma, lymphoma, uremia, vitamin deficiency, amyloidosis, ischemic peripheral vascular disease, porphyria and collagen diseases. An inquiry should be made regarding recent illnesses and particularly infections. Occasionally a history of recent infectious disease in the community may point to the correct diagnosis, for instance, infectious mononucleosis. The patient's exposure to toxins such as alcohol, drugs, and occupational poisons should be determined. Each drug used should be suspected. The possibility of arsenic or thallium poisoning should be considered, particularly if there is marital discord, if the patient is depressed or if someone in the family is known to be psychotic. Inquiry should be made regarding a family history of diabetes mellitus and porphyria, and of any neurologic syndrome similar to that of the patient. The examiner should be wary of the patient's explanation of the cause of neurologic disorders within the kinship. Commonly patients with hereditary neuropathy do not recognize the similarity of their disorder to that of others in the kinship because the disease has been attributed by the family to an accident, polio or something else. Occasionally a history of foreign travel or of military service in the tropics may lead to the correct diagnosis. In our cases of peripheral neuropathy, my colleagues and I seldom have found dietary histories enlightening, except for those from alcoholics, food faddists and the elderly. Finally, when the neuropathy comes on very gradually, the patient may not have symptoms, despite significant sensory or motor impairment, and only examination will reveal the disease.

Special Studies. In most cases of polyneuropathy, special studies are needed to determine a specific diagnosis, especially when the polyneuropathy precedes other clinical manifestations of systemic disease. But unfortunately, even with the advantage of such findings, the cause may go undiagnosed. The tests to be ordered depend on what diagnostic possibilities are suggested by the history and routine determinations. In our practice the following laboratory tests frequently are employed to detect the cause of a case of polyneuritis: tests of glucose metabolism, for diabetes mellitus; determinations of blood urea and creatinine, for uremia; the LE clot test, for disseminated lupus erythematosus; analysis of gastric acidity and Schilling's test, for pernicious anemia; determinations of stool fats and blood carotene, for the malabsorption syndrome; serum electrophoresis and bone-marrow studies, for multiple myeloma; determinations of urine porphobilinogen and other porphyrins, for acute intermittent porphyria; measurements of urinary lead, arsenic, thallium and mercury for accidental, suicidal or homicidal poisoning; serum protein and sulfobromophthalein determinations in alcoholics; and heterophile antibody determination, for infectious mononucleosis. Less frequently obtained tests include analysis of phytanic acid, for Refsum's disease; urinary sulfatide determination, for metachromatic leukodystrophy; and α and β-lipoprotein determinations, for Tangier disease and for the Bassen-Kornzweig syndrome, respectively. In some cases an intensive search for carcinoma of the lung, breast, ovary, kidney or gastrointestinal system may be indicated.

Ways of Classifying Peripheral Neuropathy

The peripheral neuropathies can be classified in several ways. On the basis of their courses, they can be divided into acute, subacute and chronic categories—or into progressive and relapsing. A course with rapid onset, a peak within a few weeks or months and then gradual improvement is seen in the Guillain-Barré syndrome, an attack of porphyria, reaction to toxic exposure, brachial plexus neuropathy and lumbosacral plexus neuropathy. A more abrupt onset, suggesting vascular occlusion, may be seen in ischemic neuritis, periarteritis nodosa, femoral neuropathy and the third cranial nerve paralysis in diabetes mellitus. An insidious onset and progressive course is seen in diabetes mellitus, various hereditary polyneuropathies, uremia, amyloidosis, carcinoma and multiple myeloma. A relapsing course is seen in chronic neuropathies of unknown cause, Refsum's disease, Tangier disease and some cases of hypertrophic neuropathy.

On the basis of predominant symptoms, the peripheral neuropathies can be divided into motor, sensory, mixed and autonomic. On the basis of the distribution of nerves affected, the neuropathies might be divided into mononeuritis (one nerve affected), mononeuritis multiplex (isolated nerve trunks affected at different times and in different regions) and diffuse peripheral neuropathy. In addition, they may be divided into disorders of the dorsal root ganglion cell, autonomic ganglion cell, root, plexus and peripheral nerve.

The peripheral neuropathies can be classified also by the nature of the pathologic alterations seen at nerve biopsy or at postmortem examination. In parenchymatous neuropathies the primary disorder

lies within nerve fibers, whereas in interstitial neuropathies it lies in the supporting tissue between the nerve fibers.

Another separation based on pathologic change can be made by the type of the myelinated fiber degeneration. In axonal degeneration (some authors also use "wallerian degeneration" synonymously), the axis cylinder degenerates first, with resultant collapse of the myelin sheath. The sequence of histologic events in this type of fiber degeneration is seen particularly well after severance or crushing of a nerve. In segmental demyelination the myelin sheath is affected without degeneration of the axis cylinder. The earliest degeneration of the myelin sheath occurs in regions near nodes of Ranvier. In more severe involvement the myelin sheath of an entire internode degenerates, leaving the axis cylinder bare. Since the myelin sheath is made up of closely wrapped Schwann cell membrane, this type of degeneration implies disease of Schwann cells.

Segmental demyelination is a predominant feature in lead and diphtheritic neuropathy, hypertrophic neuropathy of the Charcot-Marie-Tooth type and of the Dejerine-Sottas type, metachromatic leukodystrophy, the Guillain-Barré syndrome, chronic progressive polyneuropathy with excessive cerebrospinal fluid (CSF) protein, and congenital polyneuropathy with arthrogryposis multiplex. In nerves from persons with these disorders, wallerian degeneration is seen also. Axonal degeneration is seen in arsenic poisoning, periarteritis nodosa, the neuronal types of Charcot-Marie-Tooth disease, amyloidosis and multiple myeloma, and also in the vinca alkaloid neuropathies.

Another histologic characteristic of certain kinds of neuropathy is that the peripheral nerves are larger and firmer than normal. Palpation may reveal this, though in some cases planimetric measurements of transverse sections of such nerves are needed to prove enlargement. The hallmark of hypertrophic neuropathy, however, is the onion-bulb formation. The lamellae of this bulb are made up of circumferentially directed Schwann cell processes which are separated by longitudinally directed collagen fibrils. The lamellae of the onion bulb usually surround a myelinated fiber which shows evidence of segmental demyelination and remyelination. Hypertropic neuropathy is not specific for one disease and is seen in one type of Charcot-Marie-Tooth disease, in Dejerine-Sottas disease, and in Refsum's disease. It has also been found in acromegaly and in diabetes mellitus.

TABLE 1.—*Nonfocal Peripheral Neuropathies*

- Dorsal-root ganglion-cell disorders
  - Hereditary sensory radicular neuropathy
  - Congenital sensory neuropathy
  - Congenital insensitivity to pain with anhidrosis
  - Riley-Day syndrome
  - Carcinomatous sensory neuropathy
  - Progressive degeneration of dorsal-root ganglion cells without carcinoma
  - Episodic degeneration of dorsal-root ganglion cells
  - Friedreich's ataxia
  - Herpes zoster
- Peripheral-nerve disorders
  - With predominantly motor symptoms
    - Guillain-Barré-Strohl syndrome
    - Subacute and chronic polyneuropathy with increased cerebrospinal-fluid protein
    - Chronic relapsing polyneuropathy
    - Infectious mononucleosis
    - Acute intermittent porphyria
    - Hypertrophic neuropathy
      - Charcot-Marie-Tooth type
      - Dejerine-Sottas type
      - Refsum type
      - Other types
    - Lead neuropathy
    - Diphtheritic neuropathy
  - With predominantly sensory symptoms
    - Leprosy
    - Vitamin B deficiency
    - Effects of medication
    - Diabetes mellitus
    - Arsenic
    - Ischemic neuropathy
    - Uremia
    - Multiple myeloma
    - Amyloidosis

Scheme of This Presentation. The various types of nonfocal peripheral neuropathies will be discussed in this section (Table 1). In the first group of disorders the primary site of involvement is in dorsal root ganglion cells, and in the other two groups it is in the mixed peripheral nerves. The emphasis and space given the several categories of disorders have been determined by the new developments related to them, rather than proportioned to their incidence.

Dorsal-Root Ganglion-Cell Disorders

In the first group of neuropathies, the primary site of disorder is the dorsal root ganglion cells, with secondary axonal degeneration affecting nerve fibers in posterior columns and in peripheral nerves. Muscle strength and size are unaffected. Tendon reflexes are reduced or absent, because of interruption of the reflex arc.

Hereditary Sensory Radicular Neuropathy. A dominantly inherited disorder, hereditary sensory radicular neuropathy has been designated variously as the perforating foot ulcers of Hicks, mutilating acropathy and lumbosacral syringomyelia. The recognized onset of the disorder may be a blackened crust over the head of the first metatarsal bone, which breaks down to form an ulcer that is not always painless. The ulcer heals as the patient rests in bed, but it often recurs when the patient becomes ambulatory. Because of recurring foot ulcers, osteomyelitis and extrusion of bony fragments, the foot may be progressively shortened until only a stump is left. In spite of significant disability from foot ulcers, patients with this disease may live to old age. Although all sensory modalities usually are involved, perception of pain and temperature may be especially affected.

Occasionally kinships are seen which, in addition to hereditary sensory neuropathy, have an associated neurogenic peroneal muscular atrophy.

Congential Sensory Neuropathy. In a Quebec kinship, three of five siblings with unaffected parents had sensory abnormalities from infancy that made them unable to recognize objects by touch and insensitive to painful stimuli. They were clumsy, and the bones of their feet tended to break easily. There was severe sensory loss in the distal portions of all limbs. The strength and size of muscles were normal. The results of motor conduction velocity measurements and of needle-electrode examination of muscles were normal. In electrophysiologic and histologic studies of the sural nerve, there was a striking correlation between the absence of alpha and delta waves of the compound action potential and the absence of both large and small myelinated fibers. A small C fiber potential was recorded, and the unmyelinated fibers found in the nerve were smaller than normal.

Congenital Insensitivity to Pain With Anhidrosis. Two siblings described by Swanson, Buchan and Alvord showed mental retardation, insensitivity to painful stimuli and lack of sweating. Their disorder differed from the congenital sensory neuropathy just described in that the sensory loss was limited to pain and temperature and affected the entire body. On postmortem examination it was concluded that there was a selective absence of small dorsal root ganglion neurons, absence of small myelinated fibers in the root, absence of Lissauer's tract and reduction in the size of the spinal tract of the trigeminal nerve and paucity of small fibers in it. The investigators postulated a genetically determined defect in differentiation and migration of neural crest elements early in embryogenesis.

These two patients were not able to distinguish sharp from dull, and thus were quite different from those having congenital indifference to pain. The latter can tell sharp from dull and hot from cold, though they do not experience pain.

Riley-Day Syndrome. The disorder known as Riley-Day syndrome is inherited recessively and is seen especially in Jewish families. Autonomic disturbances are revealed by blotchy skin, inability to secrete tears, postural hypotension and hypertension with excitement. Tendon reflexes are absent. In addition, the children affected may be insensitive to painful stimuli. The precise anatomic and metabolic defect is not known.

Carcinomatous Sensory Neuropathy. Severe distal sensory loss in the limbs, lancinating pain and clumsiness make up a disorder that is called carcinomatous sensory neuropathy because—more frequently than expected by chance—a carcinoma develops with it or subsequently. Most often this is a bronchogenic carcinoma. Denny-Brown showed that the dorsal column demyelination and the wallerian degeneration of the axons of peripheral nerves were secondary to the degeneration of the dorsal root ganglion cells. Parenteral administration of vitamins has not ameliorated the disorder.

Progressive Degeneration of Dorsal-Root Ganglion Cells Without Carcinoma. A progressive degeneration of dorsal root ganglion cells has also been seen without associated carcinoma. Its cause and prognosis are not known.

Episodic Degeneration of Dorsal-Root Ganglion Cells. The sensory syndrome has been seen infrequently at our institution. The onset of an episode is abrupt and associated with a sensory deficit which persists. The results of the clinical examination and sural nerve biopsy (studied by quantitative histologic and teased fiber measurements) are best explained by selective degeneration of dorsal root neurons without evidence of regeneration.

Friedreich's Ataxia. In Friedreich's ataxia, a recessively inherited disorder which will not be described in detail here, there is also an early selective degeneration of the dorsal root ganglion cells. Quantitative histologic measurements of transverse sections show that large fibers are selectively decreased in number.

Herpes Zoster. This well-known disorder will not be discussed here.

Peripheral-Nerve Disorders

Disorders With Predominantly Motor Symptoms

Guillain-Barré-Strohl Syndrome. Under this eponym we include syndromes also called acute ascending paralysis or Landry's paralysis, acute febrile neuritis, acute infective polyneuritis, infective polyneuritis and infectious polyradiculoneuropathy. See the article by Wiederholt and co-workers for discussion of the historical aspects of this disorder.

There is considerable disagreement regarding etiology, criteria for diagnosis, and prognosis. According to Osler and Sidell, this diagnosis should be limited to a disorder which (1) often follows an infection, (2) occurs in both sexes, (3) is not associated with fever, (4) often begins with dysesthesias of feet or hands followed by symmetric weakness of upper and lower extremities, (5) is associated with areflexia, (6) is without much sensory loss, (7) is not related to bladder disorders, (8) is often associated with cranial nerve (particularly seventh nerve) involvement, (9) is associated with increased CSF protein but fewer than 10 cells per cubic millimeter and (10) does not leave serious residua beyond 6 months. In my opinion, however, these rather rigid criteria separate cases that essentially are alike.

Increasingly it appears that the syndrome can arise from different causes, although some authors list an unknown cause as one of the criteria for the diagnosis. According to Leneman, a variety of infections, allergic and immune diseases, endocrine and metabolic disorders, and toxic and miscellaneous states are associated with the development of this syndrome.

From the viewpoint of the practitioner, it is well to realize that patients may present with the clinical features and course of Guillain-Barré and yet have a discoverable underlying cause—for instance, infectious mononucleosis or porphyria. Furthermore, it would be a serious error to assume that the syndrome of Guillain-Barré disease will have a benign course. Not infrequently respiratory failure, fluid and electrolyte disturbances, and other problems become life-threatening. Finally, illnesses whose initial episode is indistinguishable from the Guillain-Barré syndrome may go on to a prolonged course, or recovery may remain incomplete, or indeed the episode may be repeated.

An autoimmune mechanism may underlie the syndrome. Melnick has found that approximately 50 percent of persons with the disorder have complement-fixing antibodies to nervous tissue.

Conduction velocities in distal nerve trunks may be normal in the Guillain-Barré syndrome. More usually, however, the conduction velocities of nerves are generally low. We have seen no abnormality in some sural nerve biopsy samples, even with quantitative histologic and teased fibers studies; but segmental demyelination has been apparent in others.

In treatment, the main emphasis should be on the recognition and correction of respiratory failure, fluid and electrolyte disturbances and secondary infection. A patient developing the Guillain-Barré syndrome should be checked repeatedly to determine vital capacity or inspiratory force, or both, and should be considered for tracheostomy and mechanical ventilation when the vital capacity falls below 1 liter and when inspiratory force is less than 20 cm of water. The effectiveness of corticosteroids in this disorder is uncertain. In order to reduce hypersensitivity, 6-mercaptopurine has been given, with apparent improvement in one case.

Subacute and Chronic Polyneuropathy With Increased CSF Protein. In our practice we see many cases—probably as many as those of classic Guillain-Barré syndrome—in which, after an initial course which was attributed to the Guillain-Barré syndrome, there was no remission but rather an increase of the neurologic deficit. The disorder may occur at any age and in either sex. Motor symptoms and signs predominate in these cases. In a few of them, movement and static tremor of the hands and bilateral papilledema have developed during the course of the illness. The persons with this disorder have had increased CSF pressure, low conduction velocities of nerves, and a profound degree of segmental demyelination and remyelination identifiable on sural nerve

biopsy. Corticosteroid therapy apparently has had an ameliorating effect in some cases. It may be that the same pathogenic mechanism underlies this disorder, the Guillain-Barré syndrome, and chronic relapsing polyneuropathy.

Chronic Relapsing Polyneuropathy. A lengthy, relapsing course is what differentiates chronic relapsing polyneuropathy from the disorder just described, for their initial attacks may be similar. In some of these cases corticosteroids have brought improvement; and in such prolonged courses, their employment in low dosages seems indicated.

Infectious Mononucleosis. An infrequent complication of infectious mononucleosis is a polyradiculoneuropathy which may have the characteristics of the Guillain-Barré syndrome. Occasionally the pharyngeal symptoms may have been attributed to a common cold, and the correct diagnosis made only when a raised heterophile antibody titer was obtained.

Acute Intermittent Porphyria. As recently noted by MacAlpine and Hunter, one of the earliest recorded—though unrecognized—cases of porphyria was that of King George III. His attacks of insanity were associated with muscle cramps, paralysis and red urine. Additionally, a relative had a similar disorder.

Ascending paralysis due to acute intermittent porphyria usually differs from the idiopathic kind of Landry's paralysis in that there are preceding abdominal pains, nausea and vomiting, constipation, generalized painful cramps and associated delirium. Also, the disorder is dominantly inherited. The urine may have the port-wine color when voided or may develop it on standing. Sometimes the syndrome may begin with and be overshadowed by the mental symptoms. Characteristic of the disease are its relapses, which are thought to be triggered by infections, barbiturates, sulfonamides, antifungicidal agents and heavy metals. The outlook for a patient whose attack of porphyria is accompanied by acute polyradiculoneuropathy is grave. In this situation there is usually mental confusion, excessive perspiration, tachycardia and restlessness. Respiratory assistance, fluid and electrolyte replacement, and knowledgeable and intensive nursing care are indispensable. A formidable problem, especially in a hospital setting, is how to prevent these patients from receiving medicaments which will do them harm—for example, barbiturates.

Hypertrophic Neuropathy. On the basis of natural history, electrophysiologic studies, and nerve biopsies, it has been possible to separate the hypertrophic neuropathies into several categories.

The Charcot-Marie-Tooth Type. This most common kind of hypertropic neuropathy is usually inherited as a dominant trait. Onset is usually in childhood or in the second decade. The course is favorable, with a normal life expectancy. Disability is infrequent and confinement to a wheelchair is very unusual, even in far advanced cases.

The first reliable evidence of the disorder is low conduction velocity of peripheral nerves, and this is also a continuing characteristic.

Initial symptoms include pes cavus, corns and calluses, difficulty in shoe fitting and abnormalities of gait. The gait is characteristic of bilateral dropped feet and pes equinovarus. For a few patients, standing still in one place is difficult—primarily because of weakness of both dorsiflexors and plantiflexors rather than proprioceptive loss. Pes equinovarus deformities with hammer toes and occassionally scoliosis are seen.

Weakness and atrophy begin insidiously in the peroneal and small foot muscles and spread to involve other distal muscles of the upper and lower extremites. Proximal muscle weakness is unusual.

Hyporeflexia or areflexia begins with the Achilles tendon reflex. Mild to moderate sensory loss is found in the feet and lower legs, and to a lesser degree in the hands. Often the nerve trunks are slightly to moderately enlarged. In some kinships (such as those described by Roussy and Levy), affected persons have a static or movement tremor late in the course of the disorder.

The CSF protein is normal. The number of myelinated nerve fibers per unit of transverse fascicular area and also per nerve is decreased. The mean diameter of myelinated fibers is less than normal. On light and phase-contrast microscopy, distinct large onion-bulb formations are seen in transverse sections of some nerves. In other nerves these are not apparent under the light microscope, but they are revealed by the electron microscope. In teased fiber preparations, only occasional internodes of myelinated fibers have juxtanodal or complete demyelination. There is a great variation of lengths and diameters of internodes of myelinated fibers, as is characteristic of disorders featuring segmental demyelination and remyelination. In addition, a few fibers are in various stages of wallerian degeneration.

The Dejerine-Sottas Type. This uncommon type of hypertrophic neuropathy is sporadic in most cases, but in some families several siblings are affected, suggesting recessive inheritance. Characteristically, the onset of the disorder is in utero, infancy or child-

hood; and the course is progressive, with confinement to a wheelchair at the prime of life.

The disease is a severe mixed polyneuropathy, beginning with symmetric weakness of peroneal and other distal muscles but later affecting proximal muscles also. Miosis and nystagmus may appear. Sensory loss is much more profound than in the hypertrophic neuropathy of the Charcot-Marie-Tooth type and accounts for the marked ataxia which is present. Enlargement of peripheral nerves is characteristic. The CSF concentration of protein is high. Very low conduction velocity of peripheral nerves is typical. The pathologic alterations in peripheral nerves are profound. The total fascicular area of the nerve is greatly increased. The number of myelinated fibers per unit area of a transverse section and per nerve is reduced. Onion-bulb formations are prominent. All myelinated fibers show many internodes which are demyelinated. Remyelination is incomplete in most internodes, which probably accounts for the abnormal thinness of the myelin sheath.

The Refsum Type. This recessive disorder usually begins during the first two decades with night blindness and neuritic symptoms. Additionally, these patients have electrocardiographic, dermal, and bony abnormalities. The prognosis is serious. Cammermeyer showed that these patients have a hypertrophic neuropathy. Klenk and Kahlke found an inborn error of lipid metabolism and demonstrated phytanic acid in urine, serum, liver, kidney, skeletal muscle and adipose tissue.

Other Types of Hypertrophic Neuropathy. Relapsing neuropathies of unknown etiology may produce nerve hypertrophy, and often this hypertrophic neuropathy, has caused cases of various kinds to be lumped with those of Dejerine-Sottas disease. Hypertrophic neuropathy of unknown etiology developing fairly late in life may be designated as of the Roussy-Cornil type. Hypertrophic neuropathy has also been seen in acromegaly and in diabetes mellitus.

Lead Neuropathy. The ingestion of enough lead to produce neuropathy is relatively uncommon today.

Diphtheritic Polyneuropathy. A neuropathy that has become rare since the widespread immunization against the causative disease, diphtheritic polyneuropathy is characterized by diffuse effects, notably palatal paralysis and abnormalities of ocular accommodation.

Disorders With Predominantly Sensory Symptoms

Leprosy. Although leprosy may be the most common neuropathy in the world, it is only occasionally seen in temperate climates. The diagnosis should be considered if the patients—particularly army, medical and missionary personnel—have spent time in the tropics. The neural form is manifested by anesthetic areas in the distribution of a peripheral nerve *or* in a more symmetric distribution. Leonine facies, cauliflower ears and depigmented skin are further clues to the diagnosis.

Vitamin B Deficiency. One of the more commonly encountered polyneuropathies in temperate climates is that associated with alcoholism. In such cases prolonged dietary insufficiency and particularly the lack of thiamine results in sensory neuropathy. Symptoms include burning, prickling, jabbing discomfort in feet and hands. Typically the symptoms are worse when the affected part bears weight, as the foot in walking. The calves frequently are tender. Associated weakness and areflexia are also found. Helpful clues are the history and stigmata of alcoholism and stigmata of portal cirrhosis.

In pellagra there is photosensitive dermatitis, gastrointestinal upset and neuropsychiatric disorders. Burning feet, scaly rash of face and hands, glossitis and a diet deficient in green vegetables, lean meat or dairy products are characteristic.

Multiple vitamin B deficiency may be seen in prisoners of war and elderly persons who have a deficient diet. Prickling and burning of fingers and toes may be the first symptom of subacute combined degeneration of the cord. Pyramidal tract signs may be much later in development.

Effects of Medication. The vinca alkaloid drugs, used particularly in treatment for lymphoma, may produce prickling numbness in fingers and toes during the treatment period. This complication is so frequent with these drugs that it is used as a criterion for adjustment of the dosage. These drugs produce an axonal type of degeneration in peripheral nerves, both in experimental animals and in man.

Other medicaments that produce polyneuropathy include triorthocresylphosphate (TOCP), arsenical preparations (Fowler's solution), nitrofurantoin (Furadantin), isoniazid, diphenylhydantoin (Dilantin) and gold.

Diabetes Mellitus. The most common polyneuropathy in diabetes is a mixed neuropathy and is distal and symmetric. Sensory symptoms often predominate. Associated autonomic symptoms may be postural hypotension, impotence, nocturnal diarrhea, and inability to sweat. Although the syndrome is not restricted to diabetics, when seen it should at least bring to mind the possibility of diabetes.

Mulder and co-workers have shown that the conduction velocities in nerves of patients who had diabetes mellitus without symptomatic neuropathy were significantly less than those in normal subjects, indicating mild neuropathy in these diabetics.

Femoral neuropathy (which in some cases is really lumbosacral plexus neuropathy) is seen more frequently in diabetics than in other patients.

Arsenic. A history of marital discord, or of depression accompanying mixed neuropathy with prominent sensory symptoms, is suggestive of arsenical poisoning. Occasionally medicaments such as Fowler's solution may be responsible. "Moonshine" whiskey may contain arsenic. Gastrointestinal upset, scaling skin rash and Mee's lines in the fingernails are strongly suggestive. Hair (previously washed carefully to remove hair preparations containing arsenic), nail clippings and 24-hour collections of urine should be studied for arsenical content.

Ischemic Neuropathy. Gairns, Garven, and Smith in particular have studied the symptoms and the quantitative histologic alterations of nerves in cases of amputation due to peripheral vascular disease. They have designated the discomfort in this condition as ischemic neuritic pain. Its first element is a burning sensation located just beneath the skin, occurring in acute occlusion with some blood flow; and the second, which shoots up the limb, is more characteristic of prolonged ischemia. In our experience such discomfort has not been limited to this condition.

Another form of ischemic neuropathy is that due to periarteritis nodosa. Although it may occur as symmetric neuropathy, the distinctive form is a mononeuritis multiplex with isolated nerve trunk involvement in various regions and at various times.

Uremia. Since dialysis for chronic renal disease has come into more frequent use, the polyneuropathies associated with uremia have been seen more often. Usually they are sensorimotor, distal, and symmetric.

Multiple Myeloma. A parenchymatous degeneration of nerves may occur in multiple myeloma, yet not be due to infiltration by myeloma cells. Sometimes it results from deposition of amyloid. A rather severe mixed polyneuropathy may develop before recognition of the multiple myeloma. Excess of the gamma-globulin fraction on serum electrophoresis suggests the possibility of multiple myeloma. Bone marrow examination may be helpful in substantiating the diagnosis.

Amyloidosis. The dominantly inherited variety of amyloidosis, as described by Andrade, often has a distinctive history and findings. Usually in the third or fourth decade urinary and fecal incontinence develops; sexual impotence develops in men. Beginning at this time also, recognition of painful or thermal stimuli is impaired, though ability to recognize touch and joint position is preserved. The loss of sensitivity to pain and temperature may have a radicular distribution involving segments of the lower lumbar and sacral cord. In biopsies we have found that the nerves are studded with discrete amyloid deposits. In such nerves many myelinated fibers are in various stages of axonal degeneration, and unmyelinated fibers have virtually disappeared.

(The references may be seen in the original article.)

BLEEDING FROM THE UPPER GASTROINTESTINAL TRACT

G. N. Chandler, DM MRCP, Brit Med J 4(5581):723–725, December 23, 1967.*

Haematemesis and melaena are symptomatic of haemorrhage into the upper gastrointestinal tract. When such bleeding has occurred the patient will almost always volunteer the information that the blood, if it has been vomited, has come from the stomach. Occasionally the origin of the blood may not be immediately obvious—as when haematemesis occurs as an isolated symptom in a previously healthy person—and there may also be difficulty when the supposed blood vomit has not been kept to be seen by the doctor. Examination of the stools will resolve any such doubts. Haematemesis never occurs without some blood appearing in the stools, and even in the absence of melaena chemical examination of the faeces will show the presence of much more blood than could be accounted for by other means.

Incidence and Mortality

Haematemesis is one of the commonest medical emergencies that may threaten life, and of the com-

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plications of peptic ulcer it is the most frequently encountered. Estimates of the clinical incidence of haematemesis vary from a quarter to approximately a third of all patients with peptic ulcer. The tendency to bleed is about the same during the whole course of the disease, with the exception of the first year, in which it is somewhat greater. Most published series show a mortality rate of between 5 percent and 10 percent under conservative medical treatment. However, if only examples of massive haemorrhage are considered the death rate is higher. Massive bleeding is defined as haemorrhage that is accompanied by shock, a lowering of the red cell count to 3,000,000/cu. mm. or less, and a haemoglobin level below 50 percent. With these criteria of selection the mean mortality rate is about 15 percent, with a range of 4 percent to 66 percent.

Though the mortality from haemorrhage in chronic ulcer is considerably higher than in bleeding from acute lesions, the most important correlation is with age. Below 45 years the death rate is small, but it increases sharply after the age of 60; in most western countries haematemesis is steadily increasing both in frequency and severity as the age structure of communities alters with increasing numbers of older people.

Cause of Bleeding

Peptic ulcer is easily the most important cause of haematemesis and melaena, accounting for about 9 out of every 10 admissions, but rather more than a quarter of these patients have no demonstrable radiological abnormality when examined after bleeding has ceased. Nevertheless, gastroscopy or gastrocamera inspection performed in the early stages of illness will reveal the presence of an acute ulcer in over half of this group with negative x-ray findings. These lesions heal quickly, and it is in this group that aspirin consumption makes its appreciable contribution to the number of hospital admissions for upper gastrointestinal bleeding.

Haematemesis and melaena are not uncommon complications of carcinoma of the stomach, but the diagnosis has usually been made before the onset of bleeding. In these cases the loss of blood is generally small, though exceptionally, as in the ulcerating type of cancer, it may be profuse. As the blood remains in the stomach for some time before it is vomited, it is generally coffee coloured and mixed with food and mucus.

Haemorrhage from oesophageal varices is not uncommon in cirrhosis of the liver, but confusion in diagnosis may occur since there is often a dyspeptic history and sometimes an associated ulcer. Bleeding from an oesophageal growth is rarely an early symptom and a diagnosis is likely to have been made already on account of dysphagia. Likewise an aortic aneurysm leaking into the oesophagus will almost certainly have given rise to other symptoms and signs to betray its presence. Oesophageal hiatus hernia, sliding or fixed in character, is a common gastroenterological lesion, and bleeding may occur either from an associated oesophagitis or from a gastric ulcer straddling the region of constriction at the level of the diaphragm.

Certain blood dyscrasias may be associated with haematemesis and melaena, but they are infrequent causes of these symptoms. Nevertheless, when the source of bleeding is not obvious nor the history typical the possibility of an underlying haemorrhagic diathesis should always be investigated. Usually a history of bleeding elsewhere will be obtained. Anticoagulants should not be given to patients with known gastroduodenal ulceration, but nevertheless patients on anticoagulant treatment can develop acute ulceration.

Symptoms and Signs

The clinical picture in massive haemorrhage is dominated by the development of shock. The patient is pale both from blood loss and compensatory vasoconstriction. The pulse is rapid and small; there may be marked sweating. One of the first changes to be recorded is a fall in blood pressure, and repeated measurements are essential in estimating cessation of recurrence of bleeding. Restlessness may be extreme, and rapid shallow respirations are of grave import. It is usual for any ulcer pain preceding the bleeding to disappear with the onset of haemorrhage, and the persistence of pain of any severity should always suggest the possibility of concomitant perforation, a particularly lethal combination.

The management of patients with haematemesis and melaena depends to a large extent on the diagnostic probabilities, and an adequate history should be obtained either from the patient or, if he is too ill, from an informed relative. Inquiry should be made for any antecedent history suggestive of peptic ulceration, and any record of perforation or previous radiological confirmation of the existence of an ulcer is extremely valuable.

The physical examination of these patients should be undertaken with care so as not to exhaust them. The severity of the bleeding will be immediately apparent and should be confirmed by measurement of pulse rate and blood pressure. Abdominal exami-

nation must include palpation for an enlarged spleen and an epigastric mass. The existence of a collateral circulation in hepatic cirrhosis is diagnostic of this condition. Malignant disease of the stomach may suggest its presence by a palpable tumour and enlarged glands in the supraclavicular fossa. An assessment of the extent of arteriosclerotic change in older patients is important and demands examination of the superficial arteries and the fundi. Where thrombocytopenic purpura is suspected, a tourniquet test with a sphygmomanometer cuff should be carried out.

Principles of Treatment

There is no longer any controversy about the advisability of liberal feeding. Most patients tolerate bland diet extremely well, given two-hourly with sufficient fluid to correct dehydration and maintain an adequate urinary output. Confinement to bed is essential if bleeding continues and morphine 15 mg or sodium phenobarbitone 200 mg may be given to allay restlessness or anxiety. Pulse rate and blood pressure should be measured hourly and the details recorded, together with any further episode of bleeding, on a chart available at the bedside.

There can be no hard-and-fast rules on when blood transfusion is required. While determinations of blood volume would enable the clinician to assess the amount of blood lost accurately, such techniques are as yet unsuitable for routine use and reasonable indications for transfusion are a pulse rate of 110 or more or a systolic blood pressure of 110 mm Hg or less. Such patients need transfusion urgently, and prompt action is particularly important in the elderly to prevent the irreversible cerebral damage that may complicate prolonged shock. If severe anaemia is allowed to develop a compensatory increase in venous pressure leads to greater cardiac filling and improved cardiac output. This hyperkinetic phase is shown by the presence of a full, bounding pulse, raised pulse pressure, and jugular venous distension. The venous pressure also rises during the initial stages of transfusion, and though it falls again as the arterial pressure rises overtransfusion carries the risk of precipitating heart failure. Ideally part of the replacement after massive bleeding should consist of packed red cells to minimize the possibility of overloading the circulation and to reduce the risk of pulmonary oedema. Usually gastroduodenal bleeding stops within 12 or 24 hours of admission, most often permanently, and during this time 1,500–3,000 ml of blood may be given by slow drip transfusion (40 drops per minute). Occasionally there is a continuous slow loss of blood requiring intermittent transfusion, and this seems to happen most commonly in patients bleeding from acute lesions; the vessels from which an acute ulcer bleeds are mostly small and submucosal, and such bleeding lacks the dramatic quality of arterial haemorrhage from the base of a chronic ulcer. Exceptionally, chronic ulcers bleed so severely that the only hope for the patient lies in intra-arterial transfusion and immediate operation.

Transfusions of 500 ml are unnecessary and wasteful. Large volumes of blood given rapidly carry risks of citrate intoxication and hyperkalaemia. The former may lead to defective clotting and myocardial failure and it is wise to give 10 ml of 10 percent calcium gluconate intravenously after every fourth bottle of blood. Potassium intoxication carries the very real threat of cardiac arrest—particularly if bank-blood near the limit of its expiry is used—when serum potassium levels may reach 25 mEq. Warming the blood before use will encourage the return of potassium to the cells and the danger can be further diminished by the infusion of dextrose solutions. However, when such massive transfusions are in question the need for surgical arrest of haemorrhage should be urgently reviewed.

Medication other than vitamin concentrates is best avoided, though iron may be given by mouth from the start. Constipation is the rule after haematemesis and is usually well tolerated by the patient. Purgatives should not be administered, but there is no contraindication to the giving of an enema or the use of a glycerin or Dulcolax (bisacodyl) suppository.

Time in Bed

There is no reason why the patient whose course is uncomplicated should not be allowed up by the second or third day in hospital. There is no evidence that recovery after haematemesis is hastened by confinement to bed, the dangers of which are obvious, especially in older people with associated degenerative disease.

The management of bleeding from oesophageal varices consequent on cirrhosis will be considered in a separate article. Some of these patients die from haemorrhage long before the reduction of hepatic function has become a threat to life.

Though brisk continued bleeding from peptic ulcer is an indication for surgical treatment, there are a few patients in whom operation is out of the question because of severe associated disease or overwhelming senility. Nevertheless, however unpromising the prognosis may appear, neither hope nor treatment should be abandoned. Distension of the stomach

with blood clot may be an important factor preventing the atonic stomach of a shocked patient from arresting the bleeding by contraction. Emptying the stomach with a Senoran's evacuator followed by lavage with ice-cold water may help to stop bleeding. The use of a topical haemostatic such as thrombin after lavage with 1:1000 adrenaline has been advocated in the treatment of bleeding acute peptic ulcer. In such cases the stomach should first be emptied through a large bore tube and then washed with 1:1000 adrenaline; finally, thrombin in a suitably viscous vehicle as methylcellulose is instilled into the stomach. Gastric cooling has not won any wide acceptance either for the treatment of bleeding peptic ulcer or for haemorrhage from oesophageal varices using an oesophageal extension of the gastric balloon.

Early Diagnosis in Haematemesis

The difficulty of treating bleeding peptic ulcer largely concerns the detection of those patients in whom the prognosis with medical measures must be considered poor and who will bleed to death unless surgery is employed. The problem, however, is not always easily solved. Acute ulceration or erosion of the stomach or duodenum is a common lesion which usually responds well to medical treatment. Unfortunately this diagnosis is not always obvious, being largely based on negative evidence and frequently confirmed only in retrospect by a negative x-ray. The vessels from which an acute ulcer bleeds are mostly small and submucosal, and operation should be undertaken only as a life-saving measure or because a chronic ulcer is suspected.

Extragastric sources of bleeding must also be excluded before patients are submitted to surgery. The history is most valuable in achieving a correct diagnosis; thus where chronic peptic ulceration is responsible for the bleeding it will be unusual to find such a patient denying previous periodic dyspepsia with relief of his pain by food and alkalis. The shorter the history of preceding dyspepsia, the more likely is the lesion to be acute and therefore susceptible to cure by medical means alone. Unfortunately the diagnosis is not always obvious and the history often misleading.

An attempt to obtain diagnostic information in the acute stages of illness can be helpful in subsequent management, for if chronic peptic ulcer can be diagnosed with confidence surgical treatment is to be recommended for patients over the age of 50 in whom bleeding continues or recurs. The success of such a selective surgical policy has been shown by its favourable influence on overall mortality (which can be reduced to about 4 percent), and the prompt submission of suitable patients to operation is almost certainly an important factor in achieving the best results.

Early barium-meal examination has been adopted in some centres as a means of obtaining useful information. The procedure can be undertaken on the ward using a portable x-ray set and without manipulation or the need to move the patient from his bed. Combined with gastroscopy or the use of the fibrescope or gastro-camera it has proved possible to achieve a correct diagnosis of the cause of bleeding in about 80 percent of patients admitted with haemorrhage from peptic ulcer, usually within 24 or 36 hours from admission. The introduction of the fibrescope or the blind use of the gastro-camera has further minimized the interference and discomfort suffered by the patient, for, unlike gastroscopy, the procedures can be undertaken on the ward and are far less disturbing.

The importance of reaching an early decision as to the surgical treatment of haematemesis cannot be overemphasized; nevertheless, if it is decided to operate, a little time may be allowed to improve the patient's condition by blood transfusion unless bleeding is so profuse as to permit no delay. Chronic gastric ulcer is a particularly strong indication for surgery; bleeding from this source carries a high mortality under medical treatment and its operative arrest by gastrectomy is generally easier than is the surgery of bleeding duodenal ulcer. The indications for surgical intervention in haematemesis and the treatment of bleeding oesophageal varices will be discussed in further contributions to this series.

FEVER AS A MANIFESTATION OF HYPOGLYCEMIA

Emilio Ramos, MD, Eduardo Zorilla, MD, and William B. Hadley, MD,
JAMA 205(8):590–592, Aug 19, 1968.

Fever associated with severe hypoglycemia was observed on 16 occasions in 14 patients. In most instances treatment with glucose failed to bring about prompt recovery of consciousness. Evidence suggests that both fever and delay in response to treatment are related to the presence of cerebral edema which may respond to treatment when appropriate measures, such as intravenous administration of mannitol are taken.

Every physician treating diabetic patients is confronted at some time with a patient who has severe hypoglycemia. The usual manifestations are well known and include hypothermia as well as a wide variety of neurologic signs. The clinical characteristics can be perplexing if fever is present. Although hypothermia has been recorded during prolonged hypoglycemia in psychiatric patients receiving shock therapy with insulin, its occurrence is not widely recognized during similar episodes in diabetic patients, and it is not mentioned in several rather complete reviews of the symptomatology of hypoglycemia. It is the purpose of this communication to call attention to fever as a possible manifestation of severe hypoglycemia complicating the therapy of diabetes both with insulin and sulfonyl urea derivatives. The case described here illustrates the diagnostic confusion that can be caused by this sign.

Case Material

During an eight-year period, 75 diabetic patients who had come to the Joslin Clinic required hospitalization at the New England Deaconess Hospital for treatment of severe hypoglycemia. Fever, defined as more than 100 F (37.8 C) rectally, was recorded during 16 episodes of hypoglycemia in 14 patients. In no instance was there evidence of infection, but on five occasions convulsions occurred and may have contributed to the temperature elevation. Fourteen of these episodes were due to overdose of insulin, one occurred during therapy with chlorpropamide, and one during therapy with tolazamide. In this last instance the patient had been receiving phenylbutazone before taking tolazamide, and drug potentiation may have been present. The clinical findings in these patients are summarized in the Table. The elevation of temperature was noted on admission in 12 patients; in the other four it occurred four to ten hours later despite the fact that the blood glucose level had been restored to normal. The highest recorded temperature varied from 100.2 F (37.9 C) to 103 F (39.4 C), rectally, and the elevation in the entire group lasted from 4 to 48 hours (average, 20.7 hours). The febrile reaction occurred in patients of all ages and was observed in combination with all degrees of impairment of consciousness. On the other hand, some correlation was noted between duration of neurologic abnormalities and duration of fever. With one exception, none of these patients responded immediately to the administration of glucose or glycogenolytic agents, and in spite of the return of the blood glucose to normal or hyperglycemic levels, consciousness remained impaired for periods of 1 to 24 hours (average, 10.6 hours).

In some instances, the elevated temperature was an isolated finding and was only an indication for routine radiological and bacteriological studies. When fever was associated with certain neurological abnormalities, however, a clinical picture simulating meningitis, mucormycosis, cerebral hemorrhage, or other central nervous system disease was observed. The following case, which simulated cavernous sinus thrombosis of septic origin, illustrates the fact that fever related to hypoglycemia can be misleading and a cause for great concern.

Report of a Case

A 27-year-old woman (case 4) was admitted to the New England Deaconess Hospital in a semicomatose state. She was known to have had diabetes mellitus since the age of 12, and was taking insulin (6 units of insulin injection mixed with 36 units of isophane insulin suspension before breakfast, and 6 units of insulin injection mixed with 10 units of isophane insulin suspension before supper). She was in good health until the morning of her admission when she was found to be confused and disoriented. Her husband had given her 1 mg of glucagon intramuscularly after checking the blood glucose level with glucose oxidase impregnated reagent strips (Dextrostix) and finding it to be between 40 and

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Fever During Hypoglycemia in 14 Diabetic Patients

Case No.	Age (Yr), Sex	Duration of Diabetes (Yr)	Total Insulin/24 Hr (Units)	Duration of Hypoglycemia Before Therapy (Hr)	Findings on Admission: Level of Consciousness	Findings on Admission: Blood Glucose (mg/100 ml)	Highest Temperature, F (Rectal)	Duration of Temperature Elevation (Hr)	Duration of Neurologic Abnormalities (Hr)
1	80, M	7	34	6	Confused	40	101	4	0
2	12, M	2	28	4	Stuporous*	180†	101.6	24	24
3	4, F	2	24	6	Stuporous	40	101	12	3
4	27, F	16	58	8	Confused	175†	102	24	24
5	7, M	3	12	10	Confused*	40	103	6	12
6	25, F	6	46	8	Stuporous	320†	101	24	4
7	24, F	12	46	42‡	Comatose*	40	101	24	24
8	16, M	11	52	10	Confused*	60	100.2	12	10
9	78, F	12	...§	10	Comatose	34	100.2	10	1
10	16, M	13	62	4	Comatose	132†	102	24	6
11	42, F	19	52	12	Comatose*	34	102.8	48	20
12	52, M	3	...‖	18	Confused	30	101	4	4
13	3, M	0.5	22	4	Comatose	30	102.2	48	4
14a	13, M	1	76	4	Lethargic	100†	102	48	12
14b	13, M	1	44	6	Irritable	54	103.8	8	10
14c	13, M	1	54	4	Irritable	184†	102	12	12

* Patient had convulsions.
† After administration of glucose.
‡ Patient treated elsewhere prior to transfer to New England Deaconess Hospital.
§ Tolazamide administered twice daily (250 mg).
‖ Chlorpropamide administered daily (250 mg).

60 mg/100 ml. On arrival at the hospital she was given 50 ml of 50 percent dextrose solution intravenously. Following this, the blood glucose level was 175 mg/100 ml. She was still lethargic, but was able to obey simple commands and to complain of pain in the neck. On examination, her blood pressure was 117/70 mm Hg; temperature, 102 F (38.9 C), orally; and pulse rate, 90 beats per minute. A neurologic consultant noted muchal rigidity, minimal edema of the eyelids, conjunctival injection, possible proptosis, decreased corneal reflex, and abducens paralysis on the right. The right side of the neck was tender to palpation. Kernig's sign was absent. The tendon reflexes were symmetrically hyperactive and there were extensor plantar responses bilaterally.

Lumbar puncture revealed an opening spinal fluid pressure of 350 mm H_2O. The fluid was clear and colorless and contained no cells. The glucose concentration was 139 mg/100 ml; protein, 53 mg/100 ml; and chloride, 123 mEq liter. Roentgenograms of the skull showed a faintly calcified pineal gland in normal position, and the electroencephalographic record showed no abnormalities. The initial white blood cell count was 11,800/cu mm, with 87 percent neutrophils.

During the first eight hours the temperature remained elevated (100 to 102 F, orally) and the patient became less responsive despite the continuous administration of glucose intravenously. Serial blood glucose values were 154, 180, 140, and 120 mg per 100 ml. At the end of this time, early papilledema was observed and the heart rate had decreased to 60 beats per minute. Mannitol, 12.5 gm, was given by rapid intravenous injection and 12.5 gm were added to a continuous infusion of 10 percent dextrose in water. A prompt diuretic response resulted (700 ml) and there was a remission of fever during the following four hours. The patient progressively regained consciousness and in eight hours was fully alert and afebrile with blood pressure of 90/60 mm Hg; temperature, 97 F (36.1 C); and pulse rate, 80 beats per minute. The abducens paralysis on the right had improved but was still present. The following day the lumbar puncture was repeated. At this time the opening pressure was 110 mm H_2O. Cultures of blood, spinal fluid, and urine were reported to show no growth, and throat cultures showed normal flora. Complete disappearance of signs in the eyes was noted after three more days, and she was discharged continuing therapy with morning and evening doses of isophane insulin suspension.

Comment

Alterations of body temperature during episodes of hypoglycemia are common. Hypothermia is a frequent finding and is most often observed during severe hypoglycemic reactions, although Kedes and Field have shown that lowering of body temperature occurs also during otherwise totally unsuspected sporadic episodes of hypoglycemia. The cause of hypothermia in severe coma caused by hypoglycemia presumably is a dysfunction of the central nervous system, while in the milder cases, increased heat

dissipation through the skin and decreased caloric production have been implicated.

On the other hand, fever is rarely recognized in diabetic patients as a manifestation of hypoglycemia. Since it seems to occur with all degrees of impairment of consciousness, it may be a nonspecific response to stress. The role of the hypothalamus in regulating the sympathicoepinephrine mechanism during response to stress and the specific activation of this mechanism by hypoglycemia are well recognized. The effects of increased epinephrine production are calorigenic, and can be reproduced in experimental animals by stimulation of the posterior part of the hypothalamus. It seems possible, therefore, that, at least in part, hypoglycemia induces fever by stimulation of the hypothalamo-sympathetic regulated mechanisms of heat production.

One outstanding characteristic of the patients in our series was failure to regain consciousness rapidly after restoration of the blood glucose to normal or hyperglycemic levels. Horwitz has pointed out that in psychiatric patients receiving shock therapy with insulin, elevation of body temperature is usually observed in those instances in which the usual means of restoring the patient's consciousness fail. Furthermore, he states that when fever develops during hypoglycemia caused by insulin, a "prolonged-coma reaction" can be expected. This suggests that both the prolonged reaction and the elevation of temperature may be due to the same underlying mechanism.

"Prolonged-coma reactions" associated with hypoglycemia in diabetic patients occasionally are the cause of death. Postmortem examinations in these cases have shown cerebral edema as a prominent feature. It is possible that in such cases hyperthermia may be the result of brain swelling. Certainly, in the case described in this communication (case 4), the cerebrospinal fluid pressure, the signs of cerebral edema, and the hyperthermia subsided promptly after treatment with mannitol, which suggested that the fever was of central origin and was related to increased intracranial pressure.

The mortality and morbidity of prolonged hypoglycemia might be decreased with increased awareness of the possibility of cerebral edema as the explanation for a retarded response to glucose. With administration of mannitol, Hoffbrand and Sevitt produced prompt recovery to consciousness in patients who had remained in insulin-induced coma for several hours despite correction of hypoglycemia. Fever seems to be a sign with prognostic value. When it occurs, the indication for intravenous administration of mannitol or other measures for treatment of cerebral edema should be considered.

Generic and Trade Names of Drugs

Chlorpropamide—*Diabinese.*
Tolazamide—*Tolinase.*
Phenylbutazone—*Butazolidin.*
Mannitol—*Osmitrol.*

(The references may be seen in the original article.)

PENICILLINS OLD AND NEW

Gordon T. Stewart, MD, Pediat Clin N Amer 15(3):803–814, August 1968.

Penicillin G is the only natural penicillin commercially obtainable today. The many preparations of penicillin G on the market show how popular it is and how widely it is used. These preparations include tablets and injections, available in various dosage forms. Dosages range from small ones for infants up to 15 to 20 million units in severe infections, such as meningitis, endocarditis and tetanus. These preparations are effective against many gram-positive organisms, as well as gonococci and meningococci. With the disk culture preparations today, these organisms may be tested for sensitivity in all laboratories.

Phenoxymethyl Penicillin

Phenoxymethyl penicillin is stable in gastric acids and is readily absorbed in the small intestine; it therefore gives higher blood levels than penicillin G. It is useful in the treatment of bacterial infections caused by penicillin-susceptible organisms. It is especially effective against streptococci and pneumococci and is recommended for the treatment of rheumatic fever. The dosage varies from 125 to 500 mg. every four hours.

Synthetic Penicillins

In 1959, Sheehan and Henery-Logan of the United

States successfully synthesized the entire chemical structure of penicillin. During the same year an English group headed by Batchelor isolated the chemical heart of the penicillin molecule (6-amino-penicillanic acid) from the mold juice. Once these two biochemical barriers were passed, hundreds of penicillins could be made by simply adding side chains to the penicillin nucleus.

It was during the resulting period of development that allylmercaptomethyl penicillin (penicillin O, or Cer-O-cillin) appeared; it showed great potential, especially in patients allergic to penicillin G. Although the sensitive factor failed to stand up, it is still claimed to be effective against some staphylococci, streptococci and pneumococci.

The newer penicillins cannot be lumped together, for each with its different side chain has its own distinctive property. The three advantages of the newer penicillins are (1) they can resist penicillinase-producing bacteria; (2) they are effective against gram-negative bacteria and have a broader spectrum; and (3) they can be given orally because they can withstand gastric acid.

Phenethicillin Potassium. Phenethicillin potassium, the first synthetic penicillin, used only in oral medication, provides high serum levels promptly and consistently. The levels attained are higher than those with oral penicillin G or penicillin V. Phenethicillin is effective against streptococci, pneumococci, susceptible staphylococci and gonococci. The dosage varies from 125 to 500 mg. three to six times daily.

Sodium Methicillin. Sodium methicillin (Staphcillin) is available only for intravenous or intramuscular injection. It is effective against penicillin-resistant (penicillinase-producing) staphylococci, staphylococcal septicemia, bacteremia, acute or subacute endocarditis, acute osteomyelitis and enterocolitis. Among skin and soft tissue infections it provides treatment against cellulitis, wound infections, carbuncles, pyoderma, furunculosis, lymphangitis and lymphadenitis. It is also active against the respiratory infections of staphylococcal lobar pneumonia or bronchopneumonia and lung abscess. If infections of staphylococci, streptococci, pneumococci and gonococci are sensitive to penicillin G, penicillin V or phenethicillin, this drug is not recommended as a replacement.

Intramuscularly the usual adult dose is 1 gm. every four to six hours. For infants and children it is 25 mg. per kg. (about 12 mg. per lb.) every six hours. Intravenously the usual dose for adults is 1 gm. Every six hours, using 50 ml. of sterile saline solution at the rate of 10 ml. per minute. There has not been enough experience with intravenous use in infants and children for specific recommended dosage.

Warning: Methicillin sodium and kanamycin should not be mixed, because they rapidly inactivate each other. However, they are used concurrently in infants with good results.

Sodium Oxacillin. This is the second of the penicillinase-resistant penicillins. It has the advantage that it can be given orally or parenterally. Sodium oxacillin (Prostaphlin) has been found to be effective against staphylococci—both penicillin-resistant and otherwise—pneumococci and streptococci, and it is more active in vitro per unit weight than methicillin. It is especially effective against penicillin-resistant strains of Staphylococcus aureus.

Recommended dosages: for adults, capsules are supplied with 500 mg. each and should be given every four to six hours for a minimum of four or five days for staphylococcus infections. For staphylococcic septicemia a dosage of 1 gm. every four to six hours is appropriate, depending upon the severity of the infection. Children with mild to moderate infections require 50 mg. per kg. per day in four divided doses for at least five days. For more severe infections 100 mg. per kg. per day in four divided doses is necessary. Children over 40 kg. in weight should be given an adult's dosage. Oxacillin is better absorbed on an empty stomach, preferably one or two hours before meals.

Injectable dosages: for mild to moderate infections in an adult, 250 to 500 mg. every four to six hours for a minimum of five days; for staphylococcic septicemia or other severe staphylococcus infections 500 to 1000 mg. every four to six hours. Children should be given 50 mg. per kg. per day in four divided doses for at least five days. A child weighing over 50 kg. (88 lbs.) requires the adult dose. Absorption and excretion data indicate that 25 mg. per kg. per day in newborns provides adequate therapeutic levels. Oral dosages for newborns should be 50 mg. per kg. per day in equally divided doses every six hours.

Sodium Cloxacillin Monohydrate. This agent, manufactured by Bristol as Tegopen, is one of the newer penicillins, the monohydrate sodium salt of 3-(o-chlorophenyl-5 methyl-4-isoxazolyl) penicillin. It is effective against most gram-positive cocci and can be effective against staphylococci resistant to penicillin G. It is acid-resistant and is well absorbed from the gastrointestinal tract. It is also effective against pneumococci and streptococci.

Tegopen is prepared for oral administration only.

Adults are to be given 250 mg. every six hours for mild to moderate infections or 500 mg. every six hours for more severe infections. For very severe infections a larger and more frequent dosage may be necessary. Children require 50 mg. per kg. per day in divided doses every six hours. Larger doses may be necessary for more severe infections. These dosages are more effective if given one to two hours before meals. For hemolytic streptococci and for prevention of rheumatic fever and glomerulonephritis, administer for at least 10 days.

Ampicillin. Ampicillin is effective against gram-positive organisms susceptible to penicillin G, plus many gram-negative pathogens. The following organisms have been found to be sensitive to ampicillin: *gram-postive:* hemolytic and nonhemolytic streptococci, Diplococcus pneumoniae, staphylococci not producing penicillinase, clostridia, Bacillus anthracis, C. xerosis and most strains of enterococci; *gram-negative:* Hemophilus influenzae, B. fundulaformis, Neisseria gonorrhoeae, N. meningitidis, Brucella abortus, B. melitensis, Proteus mirabilis and many strains of salmonellae, shigillae and escherichiae, including those causing typhoid fever.

Ampicillin is stable in gastric acid and is well absorbed from the gastrointestinal tract. It does not resist destruction by penicillinase. Its antimicrobial action is bactericidal: only a small percentage of ampicillin is bound by serum protein. Resistant organisms, such as Proteus, Aerobacter aerogenes and Pseudomonas, may appear and cause superinfections. Some clinicians have solved this problem by alternating ampicillin and chloramphenicol. Ampicillin has been found effective in the treatment of many infections previously beyond the scope of penicillin therapy.

Ampicillin is available for oral, intramuscular and intravenous therapy. The dosage for adults is 250 to 500 mg. every six hours. For children 100 mg. per kg. per day in divided doses every six hours is recommended. In meningitis, intravenous drip should be the beginning therapy, with intramuscular sodium ampicillin using three or four doses of 100 to 200 mg. per kg. per day.

Penicillamine

Penicillamine is a chelating agent, used to promote urinary excretion of excess copper from the tissues of patients with Wilson's disease (hepatolenticular degeneration). There has been some trouble with the nephrotic syndrome in the use of penicillamine, but recent studies seem to indicate that this is only seen in the use of the DL form. Penicillamine has also been useful in cystinuria.

Penicillamine is mentioned here because it appears in medical literature more and more, and I think we will be dealing more and more with it. Pyridoxine HC1 and copper-free multivitamine should be given with it.

Sodium Nafcillin

Sodium nafcillin is sodium 6-(2-ethoxy-1-naphthamido) penicillinate. Sold commercially as Unipen, it is primarily for parenteral or oral therapy for severe infections caused by penicillin-resistant staphylococci.

It is recommended that parenteral therapy be used at first in severe infections. As soon as the clinical condition warrants, the patient should be placed on oral therapy. Intravenously, 500 mg. every four hours usually suffices; however, if the situation is very severe, double the dosage, provided observations deem it necessary. The required amount of the drug may be dissolved in 15 to 30 ml. of sterile water or sterile normal saline and injected into the tubing of an intravenous infusion. It may also be dissolved in 100 to 150 ml. and given by intravenous drip at the rate of 100 to 150 drops per minute. Intravenous administration should be used over short periods (24 to 48 hours), because of the occasional occurrence of thrombophlebitis.

Intramuscular dosage in adults is 500 mg. every six hours. If the infection is severe, an injection every four hours may be justified. In infants and children a dosage of 25 mg. per kg. (12 mg. per lb.) once or twice daily is adequate.

Orally, 250 to 500 mg. every four to six hours for mild to moderate infections in adults is recommended. In severe infections 1 gm. every four to six hours may be necessary. In children streptococcal pharyngitis has responded to a dosage of 250 mg. three times a day. Such infections should be treated for at least 10 days to prevent rheumatic fever or glomerulonephritis. Patients with pneumonia should receive 25 mg. per kg. per day in four divided doses. Oral medication should be taken in the fasting state, preferably one to two hours before meals. Treatment should be continued until temperature is normal and cultures are negative.

Hetacillin

Hetacillin is not yet on the market, being a new semisynthetic penicillin made by Beccham Research Laboratories in England and by Bristol Laboratories. Its advantages seem to be that it is effective against

both gram-negative and gram-positive bacteria. No serious adverse reactions have been found.

Combination Therapy

I have now covered most of the penicillins available to the clinician today. I have not gone into combination treatment of infections with penicillin and other antibiotics, nor have I dealt with synergistic combinations. There have been research and experimentations on this, of course. Some of the first combinations were with sulfanilamide drugs. These were quite successful and are still available to the clinician.

One of the best synergistic combinations found in research and experimentation was the combination of penicillin and streptomycin. I am very well aware of the criticism of using streptomycin in pediatrics. However, used properly, this drug can be a life saver.

I recall an inquiry in the JAMA concerning a patient who had had tularemia 15 months previously. The treatment during the 15 months was listed. The patient had been given every conceivable medication except the one that would have cured him, which was streptomycin.

At that time I was treating a number of patients with tularemia every year with streptomycin. The results were dramatic. To my knowledge there was never any impairment to the eighth cranial nerve or any permanent damage.

I recall a 5-year-old girl who came into my office one morning. She had a history of an infected tick bite in the left axilla and a temperature of 105 to 106° F. She had been ill for over two weeks. Her agglutination test showed a very high titer. She had a tremendous abscess in the area of the left axilla. She was hospitalized, and with a combination of streptomycin and penicillin therapy she made a dramatic recovery. Her temperature was normal in four days, and she went home in five days. There was proper drainage of the abscess, fluid balance was maintained and careful checks on this patient were made at all times.

Incidentally, I have treated hundreds of cases of tularemia, and I do not recall one that did not start with a tick bite. The reason for the penicillin and streptomycin combination is that these tick bites were mixed infections. I know the story of Tulare, California, where tularemia got its name, and rabbit fever, but in some areas of our country there are ticks by the millions. It is by these tick bites that most cases of tularemia develop.

We all know how the treatment of pneumonia and many other infectious diseases, including syphilis and tuberculosis, has changed in the past 20 to 25 years. There has been some reluctance to combine antibiotics in therapy. However, research and experimentations may change this, especially in chronic infections.

How Penicillin Acts Against Bacteria

Different antibiotics act in different ways in combating bacterial infections. Some are bactericidal and others bacteriostatic. Penicillin is bactericidal. The basic structure of penicillin is 6-amino penicillanic acid. The beta-lactam ring is highly reactive and quite unstable in the penicillin molecule and is responsible for the antibacterial action of penicillin. The rigid outer wall of bacteria is continuously being synthesized from within the bacterial cell. The synthesized material (organic protein) is transferred by enzyme action to the outer wall. When penicillin comes in contact with susceptible bacteria, the labile bond in the C-N linkage of the beta-lactam ring breaks. The C attaches itself to receptor sites on the transferring enzymes of the bacteria, preventing further synthesis of the outer wall. The bacteria burst and die.

Penicillinase, produced by some bacteria, coming in contact with penicillin, breaks the C-N linkage of the beta-lactam ring. The C reacts with penicillinase to form penicilloic acid. Since the C is no longer free to react with the bacterial enzyme, it becomes ineffective against the bacteria. The newer synthetic penicillins protect the C-N bond with bulky R Groups that shield the C-N bond from the penicillinase. Thus we have some of these that are penicillinase-resistant and are effective against penicillinase-producing bacteria.

Examples of Cases

I am well aware of the other antibiotics available in the treatment of infections. Perhaps a few illustrations of actual cases will illustrate this point.

Case 1. I was called out to the home of a 5-year-old girl one morning. She was unconscious, undoubtedly as a result of meningitis and she was hospitalized. Spinal tap revealed a grossly cloudy spinal fluid with increased pressure. Culture was not necessary. A plain slide made from the fluid dried, fixed and stained, showed the infection to be diplococcic meningitis.

Sodium penicillin G, 20,000 units, mixed in 1.5 ml. of normal saline, was attached to the spinal needle

at the first spinal tap. Spinal fluid was drawn into the syringe to 5 ml. and part of the contents was injected intrathecally. Fluid was aspirated and injected several times until the entire 20,000 units of sodium penicillin G had been injected. Intravenous and intramuscular sodium penicillin was given.

The patient was still unconscious and was given little chance of survival. The following day the spinal tap was repeated. The spinal fluid was clearer with less pressure. Intrathecal injection of 10,000 units of sodium penicillin was repeated. This procedure was repeated daily for 4 days. In 48 hours the patient was conscious. The spinal fluid was almost free of cells in 4 days, and the spinal tap was performed only every other day for the next 6 days. At the end of that time the spinal fluid was practically normal and the patient's temperature was normal. The patient made a complete recovery.

The spinal tap made at a different interspace each time served two purposes. It told me the progress of the patient, and intrathecal injection of penicillin speeded up her recovery.

Case 2. I was called to the home of a 40-year-old man one morning. He had been ill for about 2 weeks with a sore throat, but had not called a doctor. He called me on this day because he had a severe headache and general aches and pains, as well as a stiffness in the neck. I explained that he could be developing meningitis and should be hospitalized. He refused.

By the middle of the afternoon his wife called me to say that he was unconscious. He was hospitalized; spinal tap revealed increased pressure and a grossly cloudy fluid. A slide of the fluid was made, fixed and stained, and revealed the pathogen to be a pneumococcus. The same procedure as in the first case was carried out, and this man also made a complete recovery.

Case 3. This case, which I recently treated, deals with a complex problem and one of the newer penicillins. At 1:30 a.m. I was in the emergency room of one of the hospitals in the city, treating accident victims. The emergency room nurse asked me if I would see another patient. A man was there with his 12-year-old son, who had been developing a generalized edema for several weeks. A few years previously he had had a kidney infection. The nurse asked me if I wanted any x-rays, but I told her that what I wanted was a urinalysis and a temperature reading. The boy had a low-grade fever, and the albumin test was so remarkable that the lab technician asked me to see it. A ++++ result is no description of the amount of albumin found; it was almost like gelatin.

I hospitalized the patient and asked for a consultation by an internist and a urologist. Each took a history and did a physical examination plus complete blood and urine studies, including a urine culture. Beta hemolytic streptococci were found in the culture. The patient was started on ampicillin, a salt-free diet and other appropriate measures. His temperature subsided, but his edema and albuminuria did not improve. I decided that we were dealing not only with glomerulonephritis but also with a nephrotic syndrome.

I ordered 40 units of corticotropin intramuscularly every 12 hours and continued the ampicillin. In 24 hours the albuminuria was 25 percent improved. I was criticized by the internist, but the second consultant, who specialized in glomerulonephritis and associated impairments, called me to state that I had done the only thing to help the patient; that he, indeed, did have glomerulonephritis *and* a nephrotic syndrome.

To make a long story short, the patient made a complete recovery. His blood pressure decreased from 160 systolic, 100 diastolic, to 110 systolic, 60 diastolic. His albuminuria completely disappeared, and his edema also vanished.

The British are using ampicillin powder in suspected contaminated bowel surgery with good results. I would suggest a refinement of this procedure. A catheter can be inserted and the intravenous solution can be given as a drip or intermittently as needed. I have done this with different antibiotics, with excellent results, and the same procedure is effective in acute peritonitis. In intravenous solution form there is less danger of adhesion.

There is some controversy over the mixture of penicillin with other types of antibiotics. In septicemia in the newborn, streptococci and pneumococci used to be the common pathogenic organisms. However, a recent study revealed staphylococci, colon bacilli, Proteus and Pseudomonas aeruginosa. Septicemia was treated with vitamins, blood transfusions, oxygen and a combination of streptomycin, antistaphylococcic synthetic penicillin, chloramphenicol and colistimethate sodium.

No single antibacterial agent seems to be effective against more than two thirds of the offending organism. A combination of either penicillin or ampicillin plus kanamycin is effective on the basis of in vitro data against 95 percent of the organisms

to be found. I have not found any proof that kanamycin and the newer penicillins should not be given together. Those who wish can alternate the two antibiotics and thus not be fearful of their conflicting with or neutralizing each other.

I would like to point out a number of infections not encountered too frequently in daily practice. These respond to penicillin therapy more readily than to other antibiotics. Actinomycosis is one example. Active cases of tetanus or neglected wounds that predispose to tetanus should be treated with penicillin along with the usual treatment, including human antitoxin and hyperbaric oxygen. It is also wise to give penicillin in gas gangrene. I know of no medication that reduces swelling as rapidly as penicillin, in infections sensitive to penicillin.

Some Problems in Penicillin Therapy

Allergic reactions have become a major problem in penicillin therapy. With proper precautions a person should never be in danger from the use of penicillin. Allergic reactions vary from anaphylactic shock to hives and delayed skin reactions. A different penicillin syndrome has recently been described. A patient, after injection, becomes faint and weak, develops a headache and is dizzy. These soon disappear, and most of these patients can later tolerate penicillin. I have seen this in other types of injections, and I think it is due to the medication getting into a small blood vessel.

Treatment of Penicillin Reactions

Every office emergency room and hospital should have a special set-up for this emergency. This set-up should include suction apparatus, airways and tracheotomy trays. For immediate treatment, 1-in-1000 epinephrine in 250 to 500 ml. of normal saline drip is used intravenously. A 2-ml. syringe may be wet inside with 1-in-1000 epinephrine and blood withdrawn into it and then reinjected intravenously. Give 80 units of corticotropin muscularly immediately, and 800,000 units of penicillinase intramuscularly and a similar amount intravenously. Repeat every 8 to 12 hours if necessary. If there is no improvement, 20 percent 1-in-1000 epinephrine in 2 ml. of dexamethasone phosphate (4 mg. per ml.) may be given intravenously, or the same amount of 1-in-1000 epinephrine may be injected into the site of the penicillin injection. A tourniquet should be placed above the site of the injection of the penicillin if possible. If the patient wheezes or shows signs of lung congestion, aminophyllin should be given slowly intravenously. Oxygen should be given if the patient is cyanotic. These measures may be repeated if necessary until the patient is fully recovered.

Purification of Penicillin

Recent studies seem to indicate that many reactions to penicillin are due to impurities acquired in their manufacture. It may be that purification can eliminate most allergic reactions.

There have been some instances of cerebral irritation from large doses of penicillin, with convulsions and other central nervous system symptoms. One of these occurred in a patient receiving 40 million units of penicillin daily; the reactions cleared up when penicillin use stopped.

In giving sodium or potassium penicillin, serial electrolyte determinations should be made. There have been some instances of potassium intoxication from large doses of potassium penicillin, especially in debilitated patients. In oral penicillin therapy, changes in the intestinal flora result in a vitamin deficiency, and severe stomatitis may develop, which can be a serious problem. This can be prevented by giving vitamins orally or parenterally. When once it develops, it requires vitamins in large doses as well as good oral hygiene.

Summary

With penicillins old and new we have overcome the problem of penicillinase-producing bacteria. The range of organisms against which penicillin therapy is effective now includes many of the gram-negative bacteria. The problems of allergy have lessened, and with purification in the manufacture of penicillin, they may be reduced still further. With this progress in the development of penicillins we have a great assortment available for the treatment of various infections. They require accurate diagnosis, prompt decision in their use, proper dosage and continued treatment until the desired goal has been reached.

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(The figures and references may be seen in the original article.)

CONNECTIVE TISSUE DISEASES AND LYMPHOMAS:

CASE REPORT AND REVIEW

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Introduction

The simultaneous occurrence of two seemingly distinct, idiopathic diseases in a person has always been an interesting subject. It is a temptation to try to establish a relationship between the two or, at least, to learn more about either or both of the diseases from the association. Currently there is great interest in diseases affecting the immunologically competent cells. We have recently encountered a patient with both systemic lupus erythematosus and lymphosarcoma, and we would like to discuss his case, not only as an interesting problem but also to suggest that the association may not be entirely coincidental.

Report of a Case

A 15-year-old boy was first seen at the Lahey Clinic in July 1963 because of hematuria and arthralgias of four months' duration. For a year after a tonsillectomy at the age of 5, he had intermittent low-grade fever, lymphadenopathy, and swelling of the knees. He was then well until March 1963 when he began to have migratory arthritis involving the ankles and the metacarpophalangeal joints and a low-grade fever. He was hospitalized elsewhere, and albuminuria and microhematuria were discovered. There was no anemia and his kidney function appeared to be normal, as evidenced by intravenous pyelography and blood urea nitrogen studies. The antistreptolysin O titer and the serologic test for syphilis gave negative results. A diagnosis of glomerulonephritis was made. Because of persistent arthralgias and gross hematuria he came to the Lahey Clinic in July 1963. He was a tall, muscular, alert lad; physical findings were normal. The hemoglobin level was 11.1 gm. and the hematocrit 37 percent. White blood cell count was 4,200 (normal differential), the serum uric acid was 8.5 mg. per 100 ml. (his father had had renal calculi), and the antistreptolysin O titer was less than 100 units. The erythrocyte sedimentation rate was 45 mm. per hour (Westergren); blood urea nitrogen, 18 mg. per 100 ml.; blood glucose, 81 mg. per 100 ml.; serum cholesterol, 168 mg. per 100 ml.; and total protein was 5.8 mg. per 100 ml (albumin, 3.5 mg. per 100 ml., globulin, 2.3 mg. per 100 ml.). Two L.E. cell preparations and two fluorescent antibody tests were positive, and the chest x-ray was normal. The electrocardiogram was normal except for a P-R interval of 0.24 seconds. Urinalysis revealed microhematuria and 1.7 gm. of albumin in 24 hours. Creatinine clearance was 122 ml. per minute. A percutaneous renal biopsy was performed, revealing glomerulitis consistent with systemic lupus erythematosus.

Treatment was begun with prednisone and Plaquenil by mouth, and he became totally asymptomatic within a few days. In November 1963 his medications were 5 mg. of prednisone and 200 mg. of Plaquenil three times a day; by January 1964 there was no urinary sediment or albumin. He remained in good health except for episodes of mild generalized arthralgia and "butterfly" rash in the summers of 1964 and 1965 after somewhat lengthy exposures to the sun. Frequent examinations failed to reveal physical or laboratory abnormalities. In June 1965 his prednisone dosage was reduced to 5 mg. twice a day.

In December 1965 during semester exams at college, he began to have mild frontal headaches. Physical examination again revealed nothing abnormal. In May 1966 the headaches became more persistent, and he complained of pains around the right knee. Still no abnormalities were detected. In July 1966 he began to have severe lancinating pains in his neck, upper arms, and thighs; he complained also of recurrent numbness of the left lower lip. The pains frequently woke him at night, and he was losing weight despite eating well. Findings of physical examination were completely normal, but the erythrocyte sedimentation rate had risen from normal levels to 70 mm. per hour; it was believed that the symptoms represented a lupus neuropathy. The dosage of prednisone was increased to 25 mg. per day, but there was only transient and slight improvement in the symptoms. He then developed intermittent diplopia, his pains became more severe, and he was hospitalized for the last time in mid July 1966. He was afebrile and the only physical abnormalities were neurological. There was slight ptosis on the right side. The diplopia was related to weakness of the

right medial and superior rectus muscles. The pupillary responses were normal and there was no papilledema. A tensilon test was normal. Initially, no objective sensory findings were noted in the face despite the patient's complaint of numbness. Within a week, however, some hypalgesia was detected over the left mandible. Still later, hypalgesia was noted in the distribution of the nasociliary branch of the fifth cranial nerve.

Examination of the cerebrospinal fluid, including pressure readings and cultures, was normal. All laboratory studies were normal except for elevation of the erythrocyte sedimentation rate. The antinuclear factor test was positive only in a titer of 1:1 (which is considered normal) and two L. E. cell preparations were negative. There was no evidence of renal dysfunction.

He then began to complain of heartburn, and an upper gastrointestinal series revealed marked gastric rugal hypertrophy and at least two small gastric ulcers. These healed with appropriate conservative treatment, but the rugal hypertrophy persisted. His neurologic signs and symptoms waxed and waned despite large doses of steroids.

About a month after admission to the hospital, he developed an incomplete third cranial nerve palsy on the left; in addition, his right oculomotor nerve weakness became complete. At the same time he developed fever, cervical lymphadenopathy, and a rapidly-enlarging mass in the mid-epigastrium. A sternal marrow puncture gave normal results, but biopsy of a cervical node and the abdominal mass revealed lymphosarcoma.

The patient's general condition deteriorated rapidly, and his cranial neuropathy progressed, as manifested by numbness of the right side of his face and weakness of the twelfth cranial nerve on the right. Soon thereafter the patient became comatose and died.

Autopsy findings were as follows: lymphosarcoma involving the abdominal and thoracic lymph nodes, liver, spleen, both kidneys, lungs, pancreas, stomach, bowel, bone marrow, brain, and third cranial nerve. There were renal changes (glomerulitis) and splenic changes ("onion-skin" lesions) consistent with systemic lupus erythematosus. Adrenal cortical atrophy was present. Hematoxylin bodies were not found in any tissue.

Discussion

Connective Tissue Diseases and Lymphoma

The association of connective tissue disorders and lymphomas has been reported in the recent past. Razis et al. in 1959 reported two cases of polyarteritis nodosa, one of scleroderma, and one of probable dermatomyositis in 1,102 patients with Hodgkin's disease, but they found no cases of connective tissue diseases among 1,269 patients with lymphosarcoma and 220 with leukemia. Hench reviewed 1,000 cases of lymphoma seen at the Mayo Clinic in 1955 and 1956 and found one case of systemic lupus erythematosus with Hodgkin's disease, one with reticulum cell sarcoma, and one with lymphosarcoma. Eleven cases of rheumatoid arthritis were also found in this series. Cammarata et al. reported three patients with systemic lupus erythematosus, one of whom had Hodgkin's disease, one lymphosarcoma, and the other reticulum cell sarcoma. A fourth patient with giant follicular lymphoma was thought to have systemic lupus erythematosus, but this was not proved. Meyer zum Büschenfelde et al. carefully studied a patient with systemic lupus erythematosus and lymphosarcoma. Dubois and Tuffanelli mentioned lymphoma as the cause of death in 1 of 135 patients with systemic lupus erythematosus. Bloch et al. have called attention to the association of lymphomas with Sjögren's syndrome. Three of 62 patients with this interesting syndrome developed reticulum cell sarcoma. Talal added reports of three other patients with Sjögren's syndrome and reticulum cell sarcoma. Recently, Miller has reported the occurrence of a connective tissue disorder and a lymphoma in five patients. One patient had simultaneous onset of rheumatoid arthritis and lymphosarcoma. Two patients with Hodgkin's disease had systemic lupus erythematosus and dermatomyositis respectively. There were also two patients with reticulum cell sarcoma, one with Sjögren's syndrome, the other with rheumatoid arthritis. All of these cases, including our patient, are summarized in Table 1.

Howqua and Mackay have suggested that L. E. cells may be demonstrated in patients with lymphoma. They have reported one patient with lymphosarcoma who had 24 positive L. E. cell preparations, rheumatoid factor present in high titer, and demonstrable antinuclear factor. Another patient who was thought to have rheumatoid arthritis had no demonstrable rheumatoid factor but did have antinuclear factor and positive L. E. cell preparations and was found to have Hodgkin's disease at autopsy. One might wonder whether these patients did not, in fact, have systemic lupus erythematosus, for the absence of characteristic histologic evidence at autopsy does not necessarily exclude that diagnosis. In all except one of the cases reviewed above the systemic lupus erythematosus began before another disorder. In one

TABLE 1.—*Association of Connective Tissue Disorders and Lymphomas*

	Systemic Lupus Erythematosus	Rheumatoid Arthritis	Sclero-derma	Dermato-myositis	Polyarteritis Nodosa	Sjögren's Syndrome
Hodgkin's disease	3	11*	1	2	2	
Lymphosarcoma	5	1				
Reticulum cell sarcoma	2	1				7
Giant follicular lymphoma	1?					
Totals	11	13	1	2	2	7

* 5 "definite" rheumatoid arthritis; 2 "probable" rheumatoid arthritis; 4 "possible" rheumatoid arthritis.

case the L. E. cell preparations and the test for antinuclear factor became negative when the lymphosarcoma developed. Our patient had a positive fluorescent antibody test in 1963. Unfortunately, at that time this test was not titered, but a positive result was considered to be significant. When his lymphosarcoma developed, the antinuclear factor test was present in a titer of only 1:1 which is not considered significant. The L. E. cell preparation in our patient also became negative, but it is possible that corticosteroid therapy suppressed the tests. This observation should be sought in future cases of this type. Miller compared the prevalence of connective tissue diseases in 1,893 patients with solid tumors and 218 patients with lymphosarcoma, reticulum cell sarcoma, and Hodgkin's disease. There were ten patients in the former group (0.53 percent) and three patients in the latter (1.38 percent). Lea, in a statistical study of the association between the rheumatic diseases and the reticuloses, concluded without any question that the presence of a rheumatic disease in a person increases the probability that one of the reticuloses will develop. Unfortunately, neither the rheumatic diseases nor the reticuloses were specifically identified, so no further conclusion can be drawn from this study. Nevertheless, it would appear that of the connective tissue diseases, systemic lupus erythematosus is the most likely to be associated with a lymphoma, and that lymphosarcoma is the most likely of these to be present in lupus.

Several hypotheses have been advanced to explain this association, as follows:

(1) It is possible that neoplastic cells produce a variety of antibodies such as antinuclear factors, hemolytic factors, and so forth, and that this may occur before the cells develop lesions microscopically recognizable as lymphoma.

(2) Perhaps the development of a lymphoma results in a "weakness" of the homeostatic control of the affected lymphoid tissue, permitting the emergence of other cells carrying "forbidden" patterns of antibody.

(3) The association may represent the release of a variety of abnormal groups of immunologically competent cells ranging from those with minimal lack of response to control to those with pronounced leukemic behavior.

(4) Perhaps a prolonged state of immunologic hyperactivity and lymphoid proliferation, such as occurs in systemic lupus erythematosus and Sjögren's syndrome, predisposes to the development of lymphoma.

The role of the thymus, the possible effects of viruses and normally nonpathogenic bacteria in individuals with aberrations of their immunological mechanisms, and other theories have recently been reviewed by Fudenberg.

The true reasons for the association between the connective tissue diseases and lymphomas, if the association is indeed more than coincidence, remain hidden in our ignorance of the etiology of the individual diseases. A study comparing the incidence of lymphomas in patients with specific connective tissue disorders with that observed in suitable controls is necessary to settle the question of coincidence. Our patient provides no clues to this solution. His systemic lupus erythematosus was apparently quiet with relatively little treatment at the time the lymphosarcoma appeared.

The Renal Lesion

Our patient's renal lesion followed the usual pattern of lupus glomerulitis. It did not progress despite minimal corticosteroid therapy and, in fact, showed some histologic evidence of improvement over the three years that he was known to have such a lesion. His renal function was always normal, and urinary abnormalities were present only when his systemic lupus erythematosus was generally active in 1963.

The Neurologic Lesion

Neurologic manifestations are quite common in systemic lupus erythematosus and are seen in about 25 percent of all cases. Cranial nerve palsies are

relatively rare, however, and occur primarily in nerves supplying the extraocular muscles. Clark and Bailey reported double vision in 3 of their 100 cases, although the exact nature of the diplopia was not discussed. Dubois and Tuffanelli reported a 1 percent incidence of diplopia in 526 cases of systemic lupus erythematosus.

Pathologically, these abnormalities are thought to be caused by small intramedullary thromboses or petechial hemorrhages. Vasculitis of the vasa nervorum may occur.

Although facial paralysis and vertigo have been described, specific palsies of the remaining cranial nerves are rare in systemic lupus erythematosus.

Cranial nerve involvement is also unusual in the lymphomas; the incidence is about 1.5 percent. The distribution appears to be different from that seen in systemic lupus erythematosus however. Sparling et al. believed that cranial nerves V–IX were most frequently invaded, while in Williams' extensive tabulation cranial nerves III–VII were more commonly involved. Of all the lymphomas, lymphosarcoma is least likely to produce central nervous system manifestation; yet, when this happens, it is more likely to affect the cranial nerves than the others. Neuropathy is often related to extension from foci in the nasopharynx, cervical nodes, parotid gland, and orbit. The cranial nerve infiltration may occur intracranially or extracranially, and the meninges may also be diffusely infiltrated with or without cranial nerve involvement.

Thus, in our patient, it was reasonable to suspect that the initial third nerve palsy was related to systemic lupus erythematosus. However, once the presence of the fifth nerve involvement was objectively established, this relationship became suspect. Indeed, as the cranial nerve paralysis progressed, it was obvious that we were dealing with something other than systemic lupus erythematosus. The progressive cranial neuropathy without long-tract signs was typical of an infiltrating process in the meninges and cranial nerves such as might be seen with lymphoma.

Summary

The case of a young man who had systemic lupus erythematosus for three years and who then developed and died of lymphosarcoma is presented. A review of the recent literature suggests that this association may be more than coincidental, and hypotheses for its occurrence are discussed. Although the patient had lupus glomerulitis for at least three years, his renal function remained normal. The cranial neuropathies of lupus and lymphoma are compared and contrasted.

(The figures and references may be seen in the original article.)

ABDOMINAL TRAUMA IN CHILDHOOD

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"By permission Surgery, Gynecology & Obstetrics."

Abdominal injuries in children present a complex diagnostic and therapeutic challenge for the surgeon and are the subject of repeated review. The operative mortality rate varies between 5 and 15 percent in reported series and is highest in children sustaining either trivial blunt trauma to the abdomen or severe trauma with associated craniocerebral, musculoskeletal, and thoracic injuries. Failure to recognize promptly and treat a coexisting intra-abdominal injury is not uncommon and increases morbidity and mortality. The task of diagnosis is made more difficult when the injured child is frightened and unable to co-operate during the examination. This situation is not unusual; indeed, it is characteristic of a child with an abdominal visceral injury.

Experience with abdominal injury in children in a large community hospital where it is frequently encountered was reviewed and assessed. During a corresponding period, all fatalities recorded by the State Medical Examiner were reviewed, and the causes of death after abdominal injury were evaluated.

Material

All children less than 14 years of age who were admitted to the Rhode Island Hospital with penetrating or blunt abdominal trauma over a nine year period, beginning in January 1958, were studied.

From the Department of Surgery, Division of Pediatric Surgery, Rhode Island Hospital, Providence, Rhode Island.

In this group were 120 patients, 91 boys and 29 girls. Injuries occurred during infancy, but they were more common in the six to nine year old age group. The youngest patient was a three weeks' old infant who was stabbed by her mother in a fit of postpartem psychosis.

Blunt, or nonpenetrating, trauma accounted for 94 percent of all abdominal injuries. Penetrating wounds were found in eight patients. Five of these wounds were caused by stabbing, two by gunshot, and one by an automobile accident in which instance all of the small intestine was eviscerated, stripped of its mesentery, and gangrenous.

Trauma to pedestrians sustained from moving vehicles caused 37 percent of all nonpenetrating injuries, and 56 percent of the patients required operation. Falls accounted for 35 percent of the total number of injuries, and 20 percent of the patients were operated upon. Other recorded causes of blunt trauma were due to fighting and play injuries, including sledding accidents.

Forty-two of the 120 patients or 35 percent underwent operation. Five postoperative deaths occurred, or 12 percent, including two following penetrating injuries. An intra-abdominal injury following abdominal trauma was the cause of death in an additional 16 patients.

Diagnostic Factors

It is generally agreed that patients with penetrating abdominal wounds must undergo exploration to rule out the possibility of a visceral injury. The decision to operate on a patient who sustains blunt abdominal trauma is more difficult, but it must never influence the initial management when the possibility of visceral injury exists. Blood is immediately obtained for typing and crossmatching, and a large gauge catheter is introduced into an available vein in an upper extremity. A nasogastric tube is inserted to decompress the stomach. The vital signs must be monitored and the patient must never be left unattended. When necessary roentgenograms are obtained. An analgesic must not be given until the decision as to whether or not to operate has been made. During the course of these preparations, the patient is evaluated and a diagnosis made.

Most important is an accurate history and a physical examination by the responsible physician at the earliest possible time. He obtains a base line from which any subsequent change is assessed. The relatively large number of patients in our series with abdominal contusions reflects a policy of prompt admission and subsequent close observation. The great majority of patients with insignificant injuries showed considerable improvement within 12 to 18 hours. The persistence or progression of abdominal signs, however, strongly favored an intra-abdominal injury. This period of watchful waiting in equivocal situations did not increase the morbidity or mortality and is recommended in the alert and co-operative patient.

Substantive clinical shock, that is, a blood pressure of less than 80 millimeters of mercury and a pulse of more than 140, was found in three patients with splenic rupture and in one patient with a retroperitoneal hematoma, in addition to all patients with hepatic injuries. Seven additional patients with normal vital signs were described as pale, sweaty, thirsty, or listless. Inclusion of these patients increases the number of operative patients exhibiting peripheral vascular change to 60 percent of the total. Hemoglobin determinations on admission were deceptively normal in 23 of 29 patients with intra-abdominal injuries. The extent of blood loss and tissue destruction not reflected by the initial hemoglobin values is well known and is further supported in this study by an eventual requirement for transfusion of 250 cubic centimeters to 8 units in all but two of the operative patients.

Berman and his associates reported an elevation of the initial leukocyte count in hepatic and splenic injuries and suggested its use as a diagnostic test in patients with abdominal trauma. Williams and Wilson and their associates corroborated these findings but showed that a leukocytic response was not uncommon in patients sustaining thoracic, cranial, or skeletal injuries, and they urged caution in its use as a test of visceral injury. Whereas a leukocyte count of more than 15,000 was recorded in 51 percent of our patients with splenic, hepatic, and gastrointestinal injuries, a similar elevation existed in 31 percent of the patients with abdominal injuries not requiring exploration. The count was normal in three patients with subcapsular splenic hematoma, and four patients with hepatic rupture who were in a state of shock upon admission emphasizes that the elevation is a measure not only of the severity of injury but also of the capability of a physiologic response. At best, it is a nonspecific response to trauma.

Aside from the diagnosis of renal injuries by intravenous pyelography, roentgenographic examination of the abdomen was not decisive of visceral injury. Most common was an exaggerated gastric air bubble resulting from a combination of aerophagy

and gastric ileus. This is a nonspecific finding with abdominal trauma and was found in two patients with uncomplicated contusions of the abdominal wall. Scout films of the abdomen taken in 16 patients with splenic or hepatic injuries showed gastric dilatation in three patients, adynamic ileus in three, and splenic enlargement and indentation of the greater curvature of the stomach in one patient each. Contrary to the report of Boley and his associates, rib fractures of the left side of the lower part of the thorax are seen on occasion with splenic injuries and were found in five of our patients.

Plain films of the abdomen are generally regarded as the least informative ancillary study, and additional time should not be spent obtaining them if the decision to operate is based on clinical grounds. The films are of value, however, in detecting extraluminal gas, particularly in the presence of retroperitoneal injury in which slow leaks are not immediate clinical signs.

The accuracy of abdominal paracentesis by means of a needle varies from 75 to 90 percent in reported series of patients. Fourteen of our patients underwent a preoperative peritoneal aspiration. One false positive result was obtained when the needle entered a large retroperitoneal hematoma. Negative results were obtained in four patients with splenic injuries who underwent operation because of progressing physical signs.

The examination is of value when it is accepted as only an adjunct to diagnosis. If enteric fluid, bile, or blood is obtained, operation is mandatory despite the occasional false positive result. A negative result from aspiration means nothing. The productivity of repeated taps, four quadrant taps, and a peritoneal lavage has been improved, but these cannot replace frequent abdominal examinations as the most reliable index of injury.

Clinical Study

One hundred and twelve patients were treated for nonpenetrating injuries of the abdominal wall, kidney, and intra-abdominal viscera.

Contusions of the abdominal wall. Twenty-four patients with simple contusions had localizing tenderness and spasm of the abdominal wall in the area of injury. Trauma to the upper portion of the abdomen was often accompanied by gastric dilatation, and a history of vomiting, preceding admission, was present in six patients. Abdominal signs subsided and the well-being of the patients returned during the next 12 to 18 hours in 70 percent of the patients.

Renal injuries. Forty-eight renal injuries were encountered. Many patients were admitted directly after trauma, but almost 50 percent were seen subsequent to gross hematuria. Pain, tenderness, and spasm in the abdomen often accompanied positive findings in the flank or costovertebral angle. External evidence of trauma was present in 13 patients. Hematuria occurred in 12 of 29 patients with splenic, hepatic, or gastrointestinal injuries.

Renal trauma ranged from minor contusions to extensive injuries of the parenchyma, vascular pedicle, and pelvis. All patients admitted with hematuria underwent intravenous pyelography and the results were graded according to the classification adopted by Parkhurst and Landsteiner. Thirty-four patients had minor renal contusions, six had major renal contusions with intrarenal hemorrhage, and four had major renal contusions and intrarenal extravasation of urine. These patients were hospitalized and kept in bed until hematuria ceased, usually within a one to two week period. Hematuria recurred in two patients who did not have an enforced period of inactivity.

Major renal contusions with extrarenal extravasation and vascular pedicle injuries with nonvisualization of the kidney are the most serious form of renal trauma and were seen four times. Extrarenal extravasation follows rupture of a calix, pelvis, or ureter. The distinction was made by retrograde pyelography as soon as the general condition of the patients permitted this examination. Drainage, through the flank, of the retroperitoneal space in the area of parenchymal injury was employed successfully in patients with caliceal rupture. Closure over an internal splint with the use of sutures is necessary for the injured extrarenal pelvis or ureter. Failure to do so in one patient with a ureteropelvic tear resulted in infection and hydronephrosis, and nephrectomy was subsequently required. The result in this patient supports the general belief that the injury be localized by intravenous and retrograde pyelography and that repair with drainage proximally be carried out shortly after injury.

If the vascular pedicle is disrupted, the collecting system does not opacify, although contrast medium is excreted normally by the uninjured kidney. Two such patients were encountered. In one, nephrectomy was carried out as an emergency procedure to control retroperitoneal hemorrhage, while in the other, atrophy of the kidney was observed by retrograde pyelography five months after injury.

Congenital anomalies resulting in pathologic change in the kidney predisposes the organ to in-

jury. Two patients with congenital aberrant vessels and secondary hydronephrosis from ureteropelvic obstruction sustained renal contusions. Nephrectomy was required in one patient because of extensive parenchymal damage and pelvic hemorrhage. Hydronephrosis was reversed after the vessels were divided in the other patient.

Bladder injuries. Five of the nine patients with bladder injuries had pelvic fractures. This is a common associated observation. Cystography performed routinely in all patients with pelvic fractures and hematuria will detect an intraperitoneal or extraperitoneal rupture of the bladder before extensive urinary extravasation occurs. One patient with rupture on cystographic examination underwent cystotomy and closure of the perforation without complication.

Splenic injuries. The spleen is the most commonly injured intra-abdominal viscus. Splenectomy was performed in 22 patients, including one patient with hepatic rupture. A vertical incision of the abdomen was utilized in all patients to provide rapid access to any other injured structure. Operation was delayed for more than 24 hours in five patients in whom the initial abdominal signs were equivocal. This group included three patients with subcapsular hematoma and two others with severe craniocerebral injuries. Early diagnosis and prompt operation were supported by localized and progressive signs in the left upper quadrant and shoulder pain in more than one-half of the patients. No deaths or postoperative complications occurred in patients with isolated splenic injuries.

Hepatic injuries. Such injuries were relatively frequent and carried a high mortality rate. Three deaths occurred among the five patients with hepatic injury after blunt trauma, compared with only one death among four patients with a penetrating injury. The higher incidence in the former group is partly due to the bursting phenomenon which follows crushing injuries of the liver against the bony thorax or veretebral bodies. The cause of death in these patients was sustained hemorrhage from avulsed hepatic veins near the inferior vena cava. Bleeding from less extensive hepatic lacerations was stopped with sutures and Gelfoam® (absorbable gelatin sponge). Adequate external tubal drainage was provided and no postoperative complications occurred in the surviving patients.

Gastrointestinal injuries. Those to the gastrointestinal tract vary from 10 to 43 percent of the patients operated upon and include mesenteric lacerations and hematoma as well as intramural intestinal injury and free perforation. Intestinal perforations were found in one-half of our patients with penetrating injuries, but none of these followed blunt abdominal trauma. Although jejunal and ileal injuries are reported, reviews of blunt trauma in children indicate the prevalence of duodenal and mesenteric injuries. The relatively smaller anteroposterior dimensions and weakness of the abdominal musculature increases the likelihood of retroperitoneal damage. Two patients in our series who were operated upon had mesenteric injuries associated with a retroperitoneal hematoma, while a third patient had a partially obstructive intramural hematoma of the third portion of the duodenum.

Evacuation of the intramural hematoma has been reported to accelerate recovery, but it was not required to relieve obstruction in our patient. In this child, normal gastrointestinal function returned by the sixteenth day and earlier in the other two patients with retroperitoneal injuries. Retroperitoneal bleeding after blunt abdominal trauma is controlled by the tampon effect of the closed space, and exploration of the retroperitoneum to identify various small bleeding veins is usually futile. Treatment is directed to adequate blood transfusion and decompression of the gastrointestinal tract until bleeding stops and adynamic ileus resolves.

Pancreatic injuries. Such injuries have been reported in about 2 to 3 percent of the injured patients. Uncomplicated contusions mimic injuries to the abdominal wall and are probably more common than suspected. Diagnosis is made by a serum amylase or equivalent test. In our only patient with contusion, the amylase level returned to normal 11 days after injury. Approximately one-half of the pancreatic pseudocysts in children occur after trauma with injury to a major pancreatic duct. The diagnosis should be suspected in any patient in whom chronic abdominal pain, epigastric tenderness, or fullness develop after even minimal abdominal contusion.

Mortality Study

Approximately 1,200 instances of sudden, suspicious, or violent death a year are reported to the State Medical Examiner. Sixteen children died from an intra-abdominal injury and were selected for study. The patients admitted to the Rhode Island Hospital as well as to the other community hospitals in the state were included.

Six children with hepatic rupture which followed a vehicular injury died within hours from hemorrhagic shock, despite operative measures to control the bleeding in four patients. The trauma sustained

in each instance was severe, and additional injuries including skull fractures, pulmonary contusions, or injuries to other abdominal viscera were recorded in all but one patient.

Hepatic injuries following crushing abdominal trauma are extensive. The problem of locating the site of the hemorrhage as well as controlling it was encountered in these patients and is the most commonly reported cause of death with hepatic injury. In such situations, intermittent digital compression of the hepatic artery and portal vein provides temporary hemostasis. Hypothermia lengthens the period of time that inflow occlusion will be tolerated, and it should be instituted preoperatively in patients in whom hepatic injury is suspected. The abdominal incision can be extended across the diaphragm to expose the superior and inferior surfaces of the liver and the hepatic veins, a common site of injury after blunt trauma. Back bleeding can be controlled by placing an umbilical tape around the inferior vena cava. Persistent oozing, after extensive hemorrhage has stopped, is often caused by activation of the fibrinolysin system. Administration of fibrinogen and transfusions of fresh whole blood have reversed this phenomenon. Recent reports emphasize the prophylactic use of drainage of the common bile duct to avoid the complications of hemobilia and to provide for decompression of the biliary system in the postoperative period.

Two children admitted in a state of shock with skull fractures died and were found at autopsy to have an unsuspected splenic rupture with hemoperitoneum. A third child had a cardiac arrest while splenectomy was in progress and it could not be resuscitated. Shock should never be attributed to craniocerebral trauma until the possibility of associated abdominal injury is eliminated.

Exsanguination from a ruptured spleen is preventable, even in the presence of a head injury. The patients with such injuries, however, have unreliable abdominal signs, and paracentesis by needle may afford the only objective indication for laparotomy.

Two patients died after severe crush injuries of the lower portion of the abdomen and pelvis. In one instance, the force was so powerful that the intestine was eviscerated, stripped of its mesentery, and the entire rectosigmoid prolapsed.

An 11 year old boy sustained a cardiac arrest when he was struck by a baseball in the middle portion of the abdomen. Death was attributed to acute circulatory failure after vagocardiac inhibition.

Visceral injuries in battered children caused the death of four patients between the ages of 15 months and two years. Visceral injuries have been reported but are not as frequent as skeletal fractures, often considered the hallmark of the syndrome. The autopsy findings were strikingly similar. Generalized ecchymoses were present. An undernourished appearance was typical of abused children with skeletal or craniocerebral injuries. Tears in the root of the mesentery were accompanied by retroperitoneal hematoma and duodenal and pancreatic injuries. The central distribution of pathologic condition about a relatively fixed point is characteristic of a decelerating force, such as a punch or blow to the epigastrium. Despite their characteristic appearance, two of the patients with a history of vomiting were sent home only hours before death because the symptoms were not considered serious. These deaths may have been prevented if the entity had been suspected, or they may be prevented in any subsequent instance, if the type of injury or appearance of the child is at variance with the history given regarding the occurrence of trauma.

Summary

The results of treatment of 133 children with abdominal injuries were reviewed in a combined clinical and mortality study at the Rhode Island Hospital and the State Medical Examiners Office. Ninety-four percent of the injuries followed nonpenetrating trauma. Operation was performed in 35 percent of the patients. Five postoperative deaths were recorded, including two subsequent to penetrating injuries.

Emphasis must be placed on the persistence of abdominal signs when the diagnosis of visceral injury after blunt trauma is uncertain. An alteration in vital signs, elevation of the leukocyte count, and a positive abdominal paracentesis confirmed the clinical impression of visceral injury in about 60 percent of the patients operated upon.

The kidney was the most frequently injured structure. The severity of injury was determined by intravenous and retrograde pyelography. Only four patients showing extrarenal extravasation or vascular pedicle injury by these studies required operation. The spleen was the next most frequently injured organ, and splenectomy was performed in 22 patients without complication or death.

The close uniformity of multiple visceral or extraabdominal injuries in the 16 deaths emphasized the poor prognosis of severe injury. Exsanguination after rupture of the spleen and liver accounted for eight deaths. Operation to control hepatic bleeding was unsuccessful in four patients, while splenic rup-

ture was masked by associated craniocerebral injury in two patients.

Visceral injuries in four battered children were undiagnosed prior to death, despite the undernourished and abused appearance of the patients. Improved measures to control hepatic bleeding and greater awareness of the possibility of visceral injury in the battered child should diminish mortality after abdominal trauma.

(The figures and references may be seen in the original article.)

MEDICAL ABSTRACTS

RECENT DEVELOPMENTS IN THE STUDY AND TREATMENT OF SHOCK

Arthur E. Baue, MD FACS, Surg Gynec Obstet 127(4):849–878, Oct 1968.

Shock has always been of considerable interest and importance to the surgeon, but increased attention has been devoted to it recently. Hardly an issue of a surgical journal appears without a report or two on experimental or clinical aspects of shock. Rediscovery of unpopularized concepts, re-emphasis of what is known, and old debates such as those concerning the applicability of canine studies to man continue. With this, however, have come significant advances in the care of the patient in shock. A number of special shock units for the study and treatment of clinical problems have been developed in recent years and have also provided valuable information. The literature on shock is voluminous and excellent monographs which cover the field in depth are available. The purpose of this article is to review presently available methods of therapy and particularly some of the important recent developments.

FATAL HEMORRHAGIC PNEUMONITIS FOLLOWING HEAD INJURY

A. W. Bronwell, MD, et. al., J Trauma 8(3):449–457, May 1968.

A new syndrome has been presented, fatal hemorrhagic pneumonitis following massive head injury. This would seem to fall into the group of conditions causing acute congestion of the lungs as recently outlined by Keller, et al. As to the management of such patients, it is the authors current feeling that patients with such injuries should have a tracheostomy and receive frequent, or if necessary, continuous respiratory therapy. Furthermore, these patients should be monitored continuously using an electrocardiographic monitor similar to those used in coronary care units. If signs of vagal stimulation appear, they should be treated with massive doses of atropine. If unable to adequately inflate the lungs, curariform agents and complete control of respiration constitute at least a potentially useful tool.

Beta adrenergic blocking agents, such as Propanolol,® are potentially useful and deserve further clinical trials when these drugs become available.

The authors are currently monitoring severe head injury patients routinely with a continuous electrocardiographic monitoring device in the intensive care unit. To date, the electrocardiographic changes that have appeared in the monitored patients have proved an infallible prognosticator as to the outcome of the patient. In two recent cases, the electrocardiographic changes have appeared two to three days prior to death and no course of therapy proved to be of aid to these patients. The authors continue to feel strongly that electrocardiographic monitoring is quite necessary in the management of the patient with massive head injury.

TREATMENT OF DISSEMINATED MYCOTIC INFECTIONS

D. J. Drutz, MD, et. al., Amer J Med 45(3):405–418, Sept 1968.

Because dose-related toxicity is a regular accompaniment of amphotericin B therapy, a therapeutic approach has been utilized which allows individualization of dosage. Amphotericin was administered daily in amounts sufficient to provide peak serum levels at least twice those necessary for inhibition of the infecting fungus for a ten week period. Total doses much smaller than those generally recommended were frequently sufficient to control systemic mycotic infections.

Fifteen patients with cryptococcosis, disseminated histoplasmosis and blastomycosis have been treated

in this manner. Therapeutic results have been excellent. Eleven patients are alive and free of disease an average of twenty-four months after a single course of therapy. Two patients have died of myocardial infarction, one during therapy and the other three months after therapy. In neither case was there evidence of active fungal infection at the time of death. One patient was killed twenty-six months after the completion of amphotericin therapy for pulmonary cryptococcosis. Only one (questionable) relapse occurred in a patient with underlying malignant disease.

This therapeutic approach provides a more rational basis for administration of amphotericin B to patients with severe mycotic infections and provides guidelines for adjusting dosage in the face of impaired renal function and other underlying medical problems.

INTIMATIONS OF MORTALITY—AN APPRECIATION OF DEATH AND DYING

Charles D. Aring, MD, Ann Intern Med 69(1):137–152, July 1968.

Students of medicine receive little (if any) specific instruction in the care of the dying. This likely reflects the conflicted feelings of physicians (and society) about it. Studies reveal that physicians are afraid of death in greater proportion than patients.

The physician's role in caring for the dying has been defined by Feder: "I don't have any idea how to help a person to die, but I am sure we can do much to help a person to *live* until the time of death." This living, as any life, should entail dignity, respect, and humanity. The immediate threat of dying is isolation, a condition that a hospital, as an agent of society, does much to impose.

To be graceful among the dying requires the physician to become aware of his feelings about death. With energies neurotically encumbered, graceful use of the self is not likely. Death can be natural if we will make it so; it is not a taboo surrounded by disapproval or shame.

THE IMMUNE RESPONSE

Stuart F. Schlossman, MD, New Eng J Med 277(25):1355–1361, Dec 21, 1967.

From the experimental evidence available one can conclude that primary immunization involves the selection, proliferation and establishment of a population of immunologically competent cells with an exquisitely specific recognition system for immunogen. It appears that the anamnestic response of "conventional antibody" and the eliciting of delayed responses are similar active processes triggered by interaction of immunogen with this "receptor." The observed differences among the various immediate reactions and the delayed reaction may only reflect on the heterogeneity of antibody, the locus of the reaction and the various mechanisms that mediate tissue damage. Clearly, the characterization of events consequent to antigen stimulation, the development of technics for study of the receptors on sensitized lymphocytes and the identification of the mediators of tissue damage in the delayed reaction will provide great insight into the mechanism of delayed hypersensitivity and into the pathologic states and host defense mechanisms that involve delayed hypersensitivity reactions. For the present, however, it is reassuring to think that from the complex and yet rather superficially understood field of immunology many basic truths and unifying concepts are emerging at an accelerated rate.

ANALYSIS OF 523 MANDIBULAR FRACTURES

MAJ J. E. Salem, DC USA, et. al., Oral Surg 26(3):390–395, Sept 1968.

Data pertaining to the cause, location, number of fracture sites, comminution, and other facial bones fractured were collated for 523 mandibular fractures, not due to gunshot, reported by selected Army installations.

1. Personal altercations were responsible for 43.7 percent of the mandibular fractures, and vehicular accidents were associated with 25.8 percent of the mandibular fractures.

2. In 55 percent of mandibles fractured there was only one fracture site.

3. Comminuted mandibular fractures were reported in 18.5 percent of the patients.

4. The angle was the site most commonly fractured, with 31.3 percent of the patients suffering mandibular fractures at this site. Other common mandibular fracture sites were the condyle (27.9 percent), the anterior body (23.1 percent), and the posterior body (21.6 percent).

5. Altercations and sports most frequently caused angle fractures, whereas vehicular accidents and falls most frequently resulted in condylar fractures.

6. Other facial bones were fractured in 16.8 percent of the patients; 67 percent of these were the result of vehicular accidents.

WERNER'S SYNDROME

D. Zucker-Franklin, MD, et. al., Geriatrics 23(8):123–135, Aug 1968.

Werner's syndrome is a relatively rare familial disease and approximately 65 cases have been reported in the world literature. The patients have a typical facies and habitus. In addition, they show premature baldness, early graying of hair, exhibit sclero-poikiloderma, generalized arteriosclerosis, trophic leg ulcers and gangrene, juvenile cataracts, calcification of blood vessels, osteoporosis, metastatic calcifications, hypogonadism, and diabetes and have a high incidence of neoplastic disease. The syndrome occurs with equal frequency in males and females and first becomes manifest shortly after adolescence when the signs of early senility appear. Other noteworthy findings include consanguinity among parents and a tendency for the disease to occur in siblings. There appears to be no birth order effect and most reported cases are of European and Jewish ancestry. While the fully developed clinical syndrome may occur in more than one member of a family, other members may exhibit a variant of the condition. No definite etiology has been established, although dysfunction of various endocrine glands has been implicated. Data of autopsy findings is limited to a very few cases in the literature. The authors recently have had the opportunity to study 10 cases of Werner's syndrome, 6 of whom have come to autopsy.

RENAL GLUCOSE THRESHOLD VARIATIONS WITH AGE

W. J. H. Butterfield, MD FRCP, et. al., Brit Med J 4(5578):505–507, Dec 2, 1967.

The results of testing an age-sex stratified random sample of the Bedford population for glycosuria during glucose-tolerance tests showed that the renal threshold level is very variable, and increases with age, especially among women. Renal threshold values as low as 130 mg./100 ml. were found in young subjects and as high as 300 mg. in elderly subjects. Thirty percent of this random sample had glycosuria during the glucose-tolerance test compared with only 4% when tested after breakfast. These findings are discussed in relation to the management of diabetic patients and the planning and execution of diabetes detection surveys.

DENTAL SECTION

HUMAN CELLS AND AGING

Leonard Hayflick, Dent Abs 13(10):608, Oct 1968.

The common impression that modern medicine has lengthened the human life-span is not supported by either vital statistics or biological evidence. Advances in control of infectious diseases and of certain other causes of death have improved the longevity of the human population as a whole, but these accomplishments have merely extended the average life expectancy by allowing more people to reach the upper limit. For the general run of mankind, this still seems to be about the Biblical four-score years.

Aging and a limited life-span apparently are characteristic of all animals that stop growing after reaching a fixed, mature size. In man, after the age of 30 years there is a steady, inexorable increase in the probability of death from one cause or another; the probability doubles about every eight years as one grows older. This general probability is such that even if the major causes of death in old age—heart disease, stroke, and cancer—were eliminated, the average life expectancy would not be lengthened by much more than ten years. It would then be about 80 years instead of the expectancy of about 70 years that now prevails in advanced countries.

Many mechanisms are involved in aging of the body. Of three such aging processes at the cell level, one is a possible decline in the functional efficiency of nondividing, specialized cells, such as nerve and muscle cells. Another is the progressive stiffening with age of the structural protein collagen, which constitutes more than a third of all the body protein and serves as the general binding substance of the skin, muscular and vascular systems. A third aging process is the limited ability of fibroblasts to continue dividing.

The author has been studying cell cultures of normal human fibroblasts. Fibroblasts taken from

4-month-old human embryos and placed in a suitable growing medium double about 50 times. After reaching this limit of capacity for division, the cell population dies.

Further confirmation of the finite lifetime of human fibroblasts was achieved when such cells from adult donors were cultured. Fibroblasts from human embryos will divide in cell culture 50± 10 times, those from persons between birth and about 20 years will divide 30 ± 10 times, and those from donors over 20 will divide 20 ± 10 times.

As the population of human fibroblasts approaches the end of its lifetime, aberrations often crop up in the chromosomes.

(Hayflick, Leonard. Stanford University School of Medicine, Palo Alto, Calif. Human cells and aging. Sci Amer 218(3):32–37, Mar 1968.)

THE RUBBER DAM DILEMMA

William F. Malone and Jerry Balaty, Dent Abs 13(10):612–613, Oct 1968.

Why, after four years of exposure to the advantages of using a rubber dam in every facet of operative dentistry, do most graduating dentists abandon its use entirely? The most common reasons given to dental educators by former students are these: "Patients are not receptive to its use." "It is not compatible with ultra-speed instrumentation and takes too much time." "I practice four-handed dentistry and the high-velocity evacuator negates the need for a rubber dam." "It separates me from my patient and I lose a mode of communication." "I use it only for endodontics and an occasional gold foil restoration." None of these reasons is rational.

The rubber dam preserves precious chair time and assists the dentist in his dedication to excellence in dental restorative services by maintaining a dry visual field. Improvements in rubber dam armamentarium have further facilitated its speed in application. The rubber dam is dentistry's isolation method for the area of operation and is analogous to the sterile drape and scrubbed field employed universally by the medical profession.

A 1961 survey showed that 19.82% of the operating time in restorative dentistry is spent observing the patient's expectorate. Generally, patients are willing to undergo any constructive measure when they are informed that this will benefit their general health. Surveys have shown that use of the rubber dam reduces chair time for the operator and his patient.

The dark, heavy, or medium dam, measuring 6 by 6 inches or 5 by 5 inches, is the most widely used because of its aid to vision and resistance to tear. Clamps now are available for any specific situation. The primary caution in clamp placement is to prevent any damage to tooth substance and soft tissue. One of the most versatile and universal clamps available for multiple or single tooth inclusion is the Ivory W8A. The average distance between holes in the rubber dam should be about 3 to 3.5 mm, to prevent tissue strangulation or leakage in the long appointment. Four types of rubber dam stabilizers are available—two strap types (the Wizard and the Woodbury designs), and two frame types (the Young's and Nygaard-Ostby) which are usually employed in pedodontic, endodontic, or limited restorative work. The more stable strap retainers are used with prolonged appointments. Disposable, absorbent flannel, tucked neatly under the frame or strap, protects the face from saliva and absorbs any mouth fluid.

(Malone, William F., and Balaty, Jerry. University of Illinois College of Dentistry, Chicago, Ill. The rubber dam dilemma. Illinois Dent J 37:138–143, Mar 1968.)

PERIODONTAL MICROCIRCULATION AND THE GINGIVAL CREVICULAR FLUID

Richard Stallard, Dent Abs 13(10):623, Oct 1968.

A recent study in nine patients (Arnold and others, 1966) showed a definite positive correlation between the integrity of the microvasculature and sulcular epithelium and the presence of gingival crevicular fluid. Though the mechanisms are incompletely understood, it is apparent that irritants from the dental plaque pass in a direction counter to the crevicular fluid flow to initiate an inflammatory response.

Initially, the inflammatory reaction, with its characteristic vascular alterations, is a physiological defense mechanism. However, in periodontal disease the inflammatory response eventually becomes pathological.

Differences in the apparent pathogenicity of periodontal irritants may be systemic or genetic. A better understanding of the microvasculature and its

part in the inflammatory process is necessary to appreciate fully the intricacies of periodontal pathosis.

The alterations observed in quantity of gingival fluid flow during healing after gingival surgery may be directly related to the inflammatory state of the gingiva and the integrity of the epithelial lining of the sulcus.

(Stallard, Richard E. 6909 West Shore Drive, Edina, Minn. Periodontal microcirculation and the gingival crevicular fluid. Paradontologie & Acad Rev 2:34–45, Mar 1968.)

DIETARY HABITS AND RELATED FACTORS IN FBM CREW MEMBERS

LT J. K. Summitt, MC USN, and CDR W. R. Shiller, DC USN.

A dietary study was conducted on board the USS CASIMIR PULASKI (SSBN 633) (Blue) during patrol. Sixteen crew member volunteers provided data concerning daily food intake, daily meal and snack distributions, weekly appetite changes, weekly food preferences, pure taste thresholds and body weight values.

The eating patterns tended to change to a reduction in the number of regular meals and an increase in the number and amount of between meal snacks. The late evening "soup down" accounted for the major part of the between meal eating. Food preferences showed little change as the patrol progressed and certainly did not reflect the predilection of submariners for sweets alluded to in some previous diary type reports. Appetite and weight gain showed a positive relationship and both tended to decrease as the patrol progressed. Taste thresholds to citric acid were increased and thresholds to sucrose were unchanged as the patrol progressed.

It is concluded that the dietary patterns of submariners are not remarkably changed on patrol. The changes that do occur are difficult to relate to any one aspect of the environment; but in any event, are of a nature not considered alarming.

(Abstract by Research Work Unit: MR005.19–6024 by LT J. K. Summitt, MC USN, and CDR W. R. Shiller, DC USN.)

The opinions or assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large.

PERSONNEL AND PROFESSIONAL NOTES

ADMIRAL RAULT HONORED

Rear Admiral Clemens V. Rault, DC USN (Ret.), received the first annual Harold W. Krogh Award for outstanding contribution to the control of oral cancer, at the semi-annual meeting of the American Cancer Society, District of Columbia Division, Board of Trustees, Thursday, November 14, 1968, at the Kennedy-Warren Ballroom.

Established in memory of Harold W. Krogh, D.D.S., who, as president of the Society's D.C. Division, inaugurated new dimensions in the early detection and control of oral cancer.

Dr. Rault, who has been a volunteer of the Cancer Society for more than ten years, served for many years as a Trustee and has been active in the Society's professional education committee.

Entering the Naval Dental Corps in 1918, he voluntarily retired in 1950 as Chief of the Dental Division of the United States Navy with the rank of Rear Admiral to become Dean of Georgetown University School of Dentistry in Washington, D.C. On January 1, 1966, he retired as Dean and was appointed Dean Emeritus and assumed duties as a consultant for the Veterans Administration.

Dr. Rault received his M.S. in oral surgery at Northwestern University in 1937. He received an honorary degree, Doctor of Science, from Georgetown University in 1959, and in 1966, Loyola University of New Orleans awarded him an honorary Doctor of Science degree.

He is currently a member of the Department of Defense Dental Advisory Committee and will be a consultant for the Central Office of the Veterans Administration.

Born in New Orleans, Louisiana, he is married to the former Violet Engler, also of New Orleans. They reside in Wild Rose Shores, a suburb of Annapolis, Maryland.

JOIN THE "SMILE-IN"

February 2-8, 1969, National Children's Dental Health Week marks the third year that the Naval Dental Corps will conduct a worldwide Preventive

Dentistry Program for Children. The success of our program in the first year of operation led the Department of Defense to direct all military departments to have a children's preventive dentistry program similar to the Navy's.

Our second year, which was supported by funding for civilian hygienists and materials, proved as successful as the first year when dental officers and dental technicians voluntarily provided the support necessary. Four hundred thousand preventive dentistry procedures have been provided children of active duty and retired Navy and Marine Corps personnel since the inception of the program.

This year, as in previous years, we should make a major effort during National Children's Dental Health Week to reinforce the efforts of the American Dental Association; therefore, program planning for 1969 should begin early. To publicize your efforts and assist the American Dental Association, it is desired that as many activities as possible submit a narrative account and photographs of their program to the Bureau of Medicine and Surgery, Code 6115, by 1 March 1969.

ANNUAL NAVAL RESERVE DENTAL SEMINAR

A most successful Naval Dental Officers Seminar was held on 29 October 1968, in the Jade Room of the Fontainebleau Hotel, Miami Beach, Florida, in conjunction with the Annual Session of the American Dental Association. The presentation by the principal speaker, RADM Thomas J. Walker, III, USN, was most timely and was entitled "Naval Operations in the Gulf of Tonkin." At present RADM Walker is Deputy Commander for Plans and Programs, and Comptroller, Naval Air Systems Command, Washington, D.C. The Assistant Chief of the Bureau of Medicine and Surgery (Dentistry) and Chief of the Dental Division, RADM Edward C. Raffetto, DC USN, ably brought the reservists up-to-date through a brief description of the "Naval Dental Corps Today."

A large reception followed the seminar attended by RADM Walker and RADM Raffetto and other dignitaries including Dr. Louis M. Rousselot, Deputy Assistant Secretary of Defense, Health and Medical; RADM and Mrs. Maurice E. Simpson, DC USN, Director of Dental Activities, Fifth Naval District; RADM Francis J. Fabrizio, DC USNR, Third Vice-President of the American Dental Association; MGEN Robert A. Shira, DC USA, Assistant for Dental Service, Office of the Surgeon General; CAPT and Mrs. George J. Coleman, DC USNR, General Chairman of the Annual Session; RADM and Mrs. Alfred W. Chandler, DC USN (Ret.), and numerous naval dental officers and their wives.

AMERICAN COLLEGE OF DENTISTS CONFERS FELLOWSHIPS

Fellowships in the American College of Dentists were conferred to three naval dental officers during the forty-eighth Annual Session of the American College of Dentists at the Deauville Hotel, Miami Beach, Florida.

The new Fellows are:

RADM Maurice E. Simpson, DC USN
CAPT Walter Neal Gallagher, DC USN
CAPT Robert A. Middleton, DC USN

INTERNATIONAL COLLEGE OF DENTISTS CONFERS FELLOWSHIP

A Fellowship in the International College of Dentists was conferred to CDR Edward Paul Klecinic, DC USN, in absentia during the Annual Session of the International College of Dentists at the Carillon Hotel, Miami Beach, Florida. CDR Klecinic is currently on duty in Vietnam.

NEWLY STANDARDIZED DENTAL ITEMS

The following newly standardized dental items are now available:

6520–086–6347	WAX, DENTAL, Inlay, Regular, 1 oz:	BX	.61

Purpose: To provide a pigmented inlay wax utilized for the indirect technique of inlay and crown fabrication.

6520–935–1094	PLIERS, Dental Amalgam Reinforcement Pin, 4 7/8 inch:	EA	5.84

Purpose: To provide a suitable instrument for cutting and holding very short sections of threaded steel wire for use in the amalgam pin-reinforcement technique.

6532–926–9974	SMOCK, DENTAL OPERATING, MAN's Aqua, Large:	EA	3.45
6532–926–9975	SMOCK, DENTAL OPERATING, MAN's Aqua, Medium:	EA	3.45
6532–926–9976	SMOCK, DENTAL OPERATING, MAN's Aqua, Small:	EA	3.45

Purpose: The above items are to provide Dental Officers with knee length smocks suitable for use in dental operating procedures.

NURSE CORPS SECTION

PLAY THERAPY AND PREOPERATIVE PREPARATION

The following paper was prepared by Nurse Corps officers who attended the Pediatric Nursing Short Course at Naval Medical School, National Naval Medical Center during the period 28 October–1 November 1968. "Play Therapy and Preoperative Preparation" is one group's approach to the care of the hospitalized child. The authors of the article are: LTJG Melody King, LTJG Linda Nash, LTJG Wilma Vering and LTJG Jane Roth.

Today we know a good deal about the psychologic responses of children to hospitalization. Many potentially disturbing situations have been identified and various alleviative methods suggested. It is our desire to examine one type of situation commonly encountered on the pediatric units of the military hospital.

The majority of children that we handle are surgical patients whose stay is relatively short term. This group is predominantly made up of tonsillectomies, cystoscopies, hernioplasties, and various eye surgeries. We will discuss the preparation of the type of patient for surgery and his immediate postoperative period through the medium of play therapy. The discussion is further limited to preparation of patients between the ages of four and seven years, our feeling being that this range represents the ages most commonly presented. Further growth and development implications of other ages would involve variables that go beyond the scope of this paper.

Play is the serious business of childhood, a period free from worry, insecurity, and fears. Through play the child learns, develops personality and assimilates his culture. Play is the natural medium of self-expression in which children can act out suppressed emotions of aggression, hostility, fear, and anxiety. As has been repeatedly documented, most of the above emotions will be present in varying degrees in the hospitalized child.

Nurses and nursing auxiliary (corpsmen, aides) by virtue of their twenty-four hour presence and intimacy of contact hold the key positions for determining the environment and experiences of their patients. It is therefore encumbent on the nurse to utilize this avenue to assure a positive play experience from the outset.

As in all successful dealings among humans there must be a workable communication. Therefore basic to any attempt at play there must be a trust between the nurse and the child. It is our feeling that the initial contact should be one-to-one. The establishment of the trust or understanding should begin as soon as the patient arrives on the unit. The patient and parent should be greeted as soon as possible. For a child to have to sit and watch the unfamiliar bustle of the ward for any length of time is certainly anxiety producing. Therefore it is important to make contact with him immediately.

The child and his parents should be shown the child's bed, where his clothes can be put, the bathroom, the toys, dayroom and be introduced to his roommates. It is felt that familiarizing him with the ward right away will make admission procedures simpler and less traumatic for the child and parent.

We feel that the nurse or corpsman who admits the child should also be the one to carry out all procedures, explanations of the surgery, and be involved in the play therapy. This is just a re-emphasis of the necessity of consistent care. In talking to the child the nurse should attempt to elicit the knowledge the child has of what is going to happen to him. The first stage of preparation then, is finding out what the child knows. It is not uncommon for children to have a very non-specific idea of what is going to be "cut."

Next the initial explanation of what is going to happen to him should be undertaken, bearing in mind what the child "says" he knows. All preparatory communications should be focused on him, being aware of the fact that 50 percent of the thinking of children under six is ego-centered.

Because the child, especially the four and five-year-old attaches effective meaning to objects before he can identify them, it is important to associate objects in the hospital setting with their true meaning. This is illustrated by children in their art work as we see them drawing what they know rather than see. In explaining what will happen to the child it is useful to let him touch and handle the stethescope, blood-pressure cuff, and other items to be used. The nurse should let the patient know he will be taking a bath that night and in the morning so he will be "extra" clean. He should know he won't be able to have any food or drink after he "goes to sleep" and tell him he can have all he wants that evening. The availability of chocolate milk, coke, 7-UP, and other such liquids on the ward is helpful because children take them readily and they can be well

hydrated before they must be NPO. If the child is going to have intravenous therapy, an empty IV bottle and tubing with needle removed can be shown to the child. He can be allowed to hang it on an IV pole, shown where the water comes out and down into the tube to his arm. He may be told that this will be how he gets his food because he may not feel like eating right away.

The patient will inevitably ask about "shots." It is our feeling that this aspect should be admitted by the nurse from the point of view that more anxiety arises from an inadequate or untruthful answer than in the truth. If allowed, a plastic disposable syringe may be given to the child so he can see how it operates. It is to be utilized in the play therapy to come. The child should also be assured that his mother can see him before he goes to the operating room.

For young surgical patients it has been shown that simple drawings of the anatomy of the surgery facilitate understanding. For the Urology patient the simple outline of a man with two circles for kidneys with tubes running to the bladder and from there to the urethra could be utilized. The child is told that his urine or whatever his name for it is, goes into the two circle-like containers in his body called kidneys and that it runs down the tubes to the bladder which is like a balloon and from there down where the child sees it come out. From this point an explanation of the catheter and how it fits into the picture can be undertaken. The presence of bandages should also be explained.

At this point it may seem that this all has little to do with play therapy. However, we feel it is essential in order for the play to be effective. Our play involves all the children who will be having surgery. Before he can play with other children and exhibit real feelings through the play, he needs the one-to-one trust relationship established. Also in order for the nurse to enter into the fantasy of play she must be excepted prior to the actual acting out. This is done in all the previous preparation.

Ideally we feel the prior preparation should take place in late morning or in the afternoon. Of course this would depend on the schedule of the ward. The actual play should be after dinner, in the early evening. The children will be more familiar with the ward, the staff, and the other patients and they will probably feel free to act out their true feelings.

The value of therapeutic play is that the child's spontaneous play and non-verbal behavior give expression to his problems and conflicts and through this medium the nurse is allowed to interact with the child patient. It is this goal that we would foresee in our play.

The pre-operative children of the ward can be given nurses caps, (easily made of paper), stethescopes, syringes, flashlights, etc. in order to act out. Children can be assigned or if possible let them choose the role of the doctor, nurse, and patient. The children hopefully will "play doctor." Each will act out his role as he perceives it. The patient will give the nurse an idea of how much he has absorbed of the verbal preparation, his fears, perception of staff, and self as a patient.

If possible the game should be instituted with as little structure as possible. Supervision is necessary; however, it can be made inconspicuous if the nurse is able to assume a role. She may do this possibly by entering the game as a new nurse who wants to know what's wrong with the patient. By entering into the fantasy, the nurse can ask questions and look into the real thoughts and feelings of the child, inaccessible with direct confrontation.

It is the goal of play to find out what needs the child has that are as yet unmet. The nurse is not present to interpret extensively, rather to find out what areas regarding the impending surgery need further clarification. She will then give support accordingly.

As was stated before, we cannot lend strength to our discussion by virtue of practice. We have seen versions of our play but can only postulate the effectiveness of what we describe. It seems to hold interesting implications. It must be kept in mind that ours is a select age group and hospital problem. The initial admission orientation with establishment of contact and explanation with visual aids is required before play is begun.

It is our feeling that the possibilities for therapeutic play are there for us to utilize. We intend to implement this discussion as a training program for ward nursing staff and a preparatory program for surgical patients.

PREVENTIVE MEDICINE SECTION

MUMPS VACCINE IN DEPENDENT CHILDREN

USDHEW PHS NCDC Morb & Mort Wkly Rep 17(45):419, Nov 9, 1968.

The Public Health Service Advisory Committee on Immunization Practices meeting on 9 Oct 1968, issued the following recommendation on use of attenuated mumps virus vaccine in public health and preventive medical programs revising the initial recommendation of 1967.

Introduction

Mumps, one of the common communicable diseases, is observed with greatest frequency in young school-age children. However, approximately 15% of reported cases occur after the onset of puberty.

Overt evidence of central nervous system disease with sequelae is rare in mumps, although meningeal involvement appears to be common. Orchitis has been reported in up to 20% of clinical cases occurring in post-pubertal males. Symptomatic involvement of other glands and organs is observed less frequently. Nerve deafness is a very rare, but serious, complication of mumps.

All naturally acquired mumps infections, including the estimated 30% which are subclinical, confer durable immunity.

Live Mumps Vaccine

Live mumps vaccine is prepared in chick embryo cell culture. It produces an inapparent, non-communicable infection following administration. Since its introduction approximately 1 year ago, mumps vaccine has been given to more than 1 million persons without report of significant side reactions clearly attributable to vaccination.

More than 95% of susceptible vaccinees develop detectable antibodies after vaccination. Although titers are lower than those induced by natural infection, the pattern of antibody persistence parallels that seen following clinical mumps. The long-term duration of vaccine induced immunity is unknown but 3-year observations show continuing protection against natural infections and, in two small groups of children, antibody levels which are persisting without decline.

Recommendations for Vaccine Use

Live mumps vaccine may be used at any age from 12 months. It should not be administered to children less than 12 months old because of possible persistence of interfering maternal antibody. The vaccine is of particular value in children approaching puberty, adolescents, and adults, especially males, who have not had mumps parotitis, either unilateral or bilateral. The mumps skin test with currently available antigens is an unreliable indicator of immunity.

Since the Committee's initial statement on live, attenuated mumps vaccine in 1967, further experience with the vaccine has been accumulated. In view of evidence showing continued vaccine efficacy and safety, the Committee has modified its recommendation for limited vaccination of young children and now suggests that consideration be given to immunizing all susceptible children over 1 year of age. The Committee reaffirms its position, however, that mumps vaccination programs should not be allowed to take priority over essential ongoing health activities.

Vaccine Dose

A single dose of vaccine should be administered subcutaneously in the volume specified by the manufacturer.

Prevention of Mumps Following Exposure

It is not known whether live mumps vaccine will provide protection when administered after exposure. There is, however, no contraindication to its use at that time. Inactivated mumps vaccine and mumps hyperimmune globulin are of questionable effectiveness under these circumstances.

Precautions in Using Live Mumps Vaccine

Severe Febrile Illnesses: Vaccination should be postponed until the patient is completely recovered.

Marked Hypersensitivity to Vaccine Components: Mumps vaccine is produced in chick embryo cell culture and should not be given to persons hypersensitive to ingested egg proteins. Also, the vaccine contains small amounts of neomycin, so it should not be given to individuals known to be sensitive to this antibiotic.

Leukemia, Lymphomas, and Other Generalized Malignancies: Theoretically, attenuated mumps virus infection might be potentiated by other severe

underlying diseases, such as lymphomas and generalized malignancies.

Altered Resistance from Therapy: Steroids, alkylating drugs, antimetabolites, and radiation may predispose to untoward complications due to altered resistance.

Pregnancy: On theoretical grounds, it is reasonable to avoid using the live mumps vaccine during pregnancy.

Simultaneous Administration of Live Mumps Vaccine with Other Antigens

In order to evaluate the live mumps vaccine adequately, its simultaneous administration with other vaccines should be deferred until results of controlled clinical investigations are available. Until then, it is recommended that mumps vaccination be separated from other immunization procedures by about one month whenever possible.

EIGHTH INTERNATIONAL CONGRESS ON TROPICAL MEDICINE AND MALARIA TEHRAN, IRAN, 7–14 SEPTEMBER 1968

LT Jerold J. Yecies, MC USN, the Assistant Officer in Charge, U.S. Navy Preventive Medicine Unit No. 7, Naples, attended the Eighth International Congress on Tropical Medicine and Malaria, Tehran, Iran, which is held pentannually. Also attending were 1,200 delegates from 90 countries. The Congress consisted of a 3-hour daily morning intercongressional plenary session, and two 2-hour afternoon sessions on specific tropical medicine subjects and infectious diseases.

The plenary sessions included discussions on interaction between diseases in the tropics and socioeconomic factors, health planning and evaluation, dynamics, surveillance and control of infections, and health problems, and epidemiology of human population isolates and migratory groups. These discussions were of a general nature and included short presentations by representatives of numerous countries. Of particular interest was the seminar on surveillance which included systemic collection of pertinent epidemiologic data, consolidation and evaluation of data by the epidemiologist, and prompt dissemination of epidemiologic evaluations of current problems.

The afternoon sessions on various disease consisted of divisions on Helminthic Infections including Schistosomiasis, Filariasis, Intestinal Helminthiases; Protozoan Infections, including Amebiasis, Leishmaniasis, African and American Trypanosomiasis; Mycotic Infections, including Histoplasmosis, Coccidioidomycosis; Bacterial Infections, including Cholera, Plague, Tuberculosis, Streptococcal Infections; and Viral and Rickettsial Infections, including Rabies, Measles, Viral Hepatitis.

Other sections were presented on Spirochetal Infections, Leptospirosis, Nutritional Diseases, Tropical Hygiene and Sanitation, and Malaria. Each subject was presented for two or three sessions and included pathobiological aspects, clinical, pathological and therapeutic aspects, and epidemiology and control. Since there were 10 to 12 subjects being presented simultaneously in different rooms, it was only possible to attend 2 or 3 sessions each afternoon. Those attended were of the greatest significance for the Preventive Medicine Unit No. 7 area of operation, namely, Viral Hepatitis, Rabies, Tuberculosis, Cholera, Plague, Measles, and Amebiasis. A 1,500 page book of abstracts and reviews of the conference is available from this unit should additional information be desired.

In general, the conference was conducted on a highly professional level with experts in each field presenting and discussing information. Attendance at future congresses is highly recommended.—PrevMedDiv, BuMed.

POISONOUS SNAKE PREVENTION AND CONTROL

Snakes probably cause more alarm than any other animal, including spiders; yet the majority of snakes are beneficial and should be protected rather than destroyed.

Poisonous snakes have been reported from all mainland states except Alaska, although it is reported that they have been exterminated in Maine. Only the copperhead and 3 species of rattlesnakes have really extensive ranges. Poisonous snakes in Canada are restricted to comparatively small sections of southern British Colombia, Alberta, Saskatchewan, and Ontario Provinces. Areas with unusually large snake population include parts of the Great Plains (rattlesnakes); the lower Mississippi Valley and Gulf Coast (rattlesnakes and cottonmouths), and the southern Appalachians (rattlesnakes and copperheads). Rattlesnakes are known from elevations up to 11,000 feet in the southern Sierra Nevada of California to areas below sea level, and to the tops of the highest peaks in the Appalachians.

The 10 poisonous snakes of the United States may be divided into two distinct groups. The Coral Snake

belongs to the Cobra Group and the rattlesnakes and moccasins to the pit vipers.

The Cobra Group suggests Asia and Africa, but our 41 species of coral snakes are colorful, harmless-looking reptiles without provision for the picturesque "hood". Like other cobras, these have comparatively short fixed fangs and inject venom by biting with a chewing-rasping jaw motion until the skin of the victim is penetrated. This group is feared because of the virulent poison that rapidly attacks the human nervous system.

The color of the coral snake is rather dramatic with alternating red, yellow, and black rings around the body. This coloration and pattern is attractive to small children who have on occasion been found playing with snakes which have inadvertently crawled into play areas. It is fortunate that coral snakes are rather docile and can usually be handled for long periods without striking.

The scarlet king snake and scarlet snake, non-poisonous snakes with red, yellow and black markings on the body are often confused with the coral snake, but the pattern on the body of the former two is distinct and different. The coral snake has a slim head with a black snout, broad yellow head band, narrow yellow rings between red and black on the body, and tail with narrow yellow and wide black cross bands. The scarlet and scarlet king have red snouts and yellow rings between black rings on the body.

Coral snakes are found throughout Florida, along the Atlantic and Gulf coastal plains from North Carolina to Texas; up the Mississippi Valley to Indiana and Ohio. One species, the Arizona coral snake has adapted to semidesert areas and is found from western Texas through southern New Mexico and Arizona and northwestern Mexico.

The coral snake is a burrower that lives under litter and soil, and is frequently plowed or dug out: they venture out to feed by night or after rains.

The Pit Viper Group is characterized by a pit or hollow about halfway between the eye and nostril. All of these are stout-bodied snakes with triangular heads on slim necks. The eyes have vertical pupils. These snakes have large long fangs which are firmly attached to a small bone, which is in turn hinged to the front of the skull. Thus, the fangs are erected as the snake's mouth is opened, and folded down within a fleshy sheath as the mouth is closed. They give birth to live young in late summer. This group is similar to some vipers of the Old World without pits, but the rattlesnakes are found only in the Americas. North America pit vipers may be further divided as 2 moccasins and 15 rattlesnakes.

The copperhead or highland moccasin is distributed down the entire Atlantic and Gulf Coast, except for peninsular Florida, and westward to Texas and Illinois. They are found in hilly rocky country as well as in damp meadows. City gardeners report them in rock walls and hedges. Favorite haunts are slab-sawdust piles, under haystacks and in barns. In hot weather the copperhead is most active at night.

The cottonmouth or water moccasin inhabits swamps, shallow lakes and sluggish streams through the southern lowlands to central Texas, north to southeastern Kansas and Virginia. They are often seen basking by day on logs, stones, or branches near water. Frequently it is a belligerent snake that does not try to escape, but throws back its head with mouth widely open showing the white interior while twitching and vibrating the tail. One of the largest snakes of the South, its aggressive appearance and large head mark it as a truly sinister animal.

There are a number of non-poisonous water snakes with similar indistinct black or brown colors that may be confused with this moccasin. Unless one is sure, it is well to beware of these.

Species identification among rattlesnakes may be difficult because of the variations in color and pattern, but it is often important. The venoms show significant differences that can influence treatment and prognosis. Polyvalent Crotaled Antivenin (Wyeth Laboratories, Inc., Marietta, Pa.) is specific for the venoms of eastern and western diamondback rattlesnakes but is effective to some degree against all rattlesnake venoms.

Rattlesnakes can be almost always identified by the jointed rattle at the tip of the tail. The rattle is vestigial in a single rare species found on an island off the Mexican coast. In pigmy rattlesnakes the rattle is too small to be a good field identification character. The facial pit is present in all rattlesnakes.

Rattlers are found in desert and brush-covered country, mountainous country and the foothills, and around subdivisions located in formerly "wild" areas. They are active from the first warm days of spring until the onset of cold weather. They hibernate during the winter. When the sun is too hot or when it is chilly, the snakes seek shelter under shrubs, logs, rocks, or any other place that offers protection against the weather.

Rodents are the principal food source for the larger poisonous and non-poisonous snakes. Lizards,

toads, field mice, and insects are eaten by the smaller snakes. Therefore, it is essential to have a rodent-free environment around and in areas adjacent to residences and human habitats in order to prevent intrusion and infestations of snakes. Remove rodent harborages by piling wood 18 inches above the ground. Rubbish piles and garbage should be disposed of regularly and not left long enough to attract rodents. Grass cuttings, weeds, and tree trimmings should be removed promptly. In areas already infested with rodents, an active control campaign should be conducted to eliminate the rodent population. Technical advice and assistance for rodent control can be requested from the military entomologists at the Preventive Medicine Units and the Navy Disease Vector Control Centers or the civilian entomologist in the Area Office of the Naval Facilities Engineering Command.

Pesticides have sometimes been recommended for the control of snakes. These are not usually used specifically to kill the snakes, but are intended as a control of the food source thereby making the area unattractive for snakes. If insecticides are applied in dosages strong enough to kill snakes they can be harmful to domestic pets and small children. Such applications should be avoided. Items labeled as snake repellents or for snake control are usually nothing more than insecticides or a mixture of insecticides. Prior to using any of these materials the area entomologist should be consulted.

The following precautions should be taken for snake protection and to avoid the chance of being bitten in wooded areas or where snakes are present.

1. The hands and arms should never be put into burrows or bushes without first looking. Rocks and tree limbs should be moved with a stick before lifting them with the hands.

2. Sleeping bags should never be placed near rock piles, rubbish heaps, or near the entrance to caves.

3. Walking or gathering firewood after dark should be avoided.

4. Do not step over logs if the opposite side is not visible. Step on the log first.

5. Freshly killed venomous snakes should not be handled. Carry them on a stick or in a bag if they must be returned to the command post or medical facility for identification.

6. Crawling through high grass and bushes or uncleared areas is to be avoided when possible.

7. Walk on cleared paths as much as possible, away from rocky ledges.

8. Avoid caves, open tombs, and known snake dens.

9. A cleared strip of land, from 30 to 150 feet wide between the yard and brush-covered areas discourages snakes.

10. A fence of galvanized ¼ inch mesh hardware cloth will keep snakes out of the premises. The lower edge should be inserted 6 inches under the ground. Fit gates closely. Remove vegetation next to the fence so the snakes cannot climb up and cross over.

11. Seal openings in and under buildings. Cover ventilators.

12. Trim shrubs to provide several inches of ground clearance.

13. When looking for snakes in concealed areas, such as ivy lawn and untrimmed shrubbery, poke ahead with a stick. If the snake is there, it will either attack the stick or glide quickly out of the way. *The desire to avoid direct contact is mutual.*

14. Finally, if bitten *Do Not Panic.* Kill the snake if possible for identification. Either administer first aid or get to a medical facility as soon as possible.—PrevMedDiv, BuMed.

PRE-EXPOSURE RABIES VACCINATION EXPERIENCE WITHIN THE PEACE CORPS

Morb & Mort, Reportable Diseases, Los Angeles County Hlth Dept, Week Ending July 22, 1967.

In 44 countries around the globe, there are dispersed some 13,000 Peace Corps Volunteers. These Volunteers are widely distributed in both urban and rural situations and are often at considerable distance from medical facilities. They live in close proximity to their host country national counterparts and some in close contact with the local animal population. As a result of this mode of existence, they are presented with a significant hazard from rabies. With few exceptions, rabies is endemic in all of the host countries where Volunteers are stationed. For example, in Lima, Peru, over the past 5 years, over 47,000 dog bites have been reported. During the first 9 months of 1964, 493 rabid dogs were isolated. In Thailand, there are 200 to 230 deaths per year. In the Philippines, there are 270 deaths per year reported.

In a recent epidemiologic study, it was noted that in the United States some 362 dog bites occur per 100,000 population per year. This undoubtedly represents under-reporting. It is interesting to note that 76% of the individuals bitten were under 20 years of age. By way of comparison amongst Peace

Corps Volunteers, there are 3.20 bites per 100,000 per year, and 98% occur in individuals 20 years of age and older. It is apparent that in Volunteers, potential rabies exposure rate from dog bites approaches 10 times the United States rate, and the bites occur in an animal population that is uncontrolled.

All Peace Corps Volunteers are given 30 hours of personal health training prior to going overseas; however, the Peace Corps Volunteer does not always fully appreciate particular risks to his health. Hence, not recognizing the danger of rabies, he might neglect to report a potential exposure from an animal bite until a week or more after the exposure has occurred. It can be readily appreciated that this can create considerable anxiety amongst the members of the medical staff responsible for his safety and well being. The work of several investigators has demonstrated the feasibility of pre-exposure immuno-prophylaxis against rabies.

The program was instituted utilizing duck embryo vaccine given in a series of 3 inoculations: One cc of vaccine was given at time 0, the second inoculation was given 3 weeks later, and finally, the third inoculation was administered 3 to 6 months later. Over 5,000 individuals have been immunized by this regimen.

An important aspect in evaluating any immunization procedure is to determine the magnitude of untoward reactions to the vaccine. These data were solicited from the Peace Corps Medical Consultants at the training sites where the Volunteers are prepared for overseas service, both medically and in terms of their training. Data on 3,427 individuals were received and there were 23 reactions to the immunization procedure. Nineteen of the reactions occurred following the first inoculation. The intensity of the reaction ranged from local edema and induration to generalized anaphylaxis. Actually, only one case of anaphylaxis occurred in this group. The typical reaction was an urticarial response, though there were also many who responded with nausea and/or vomiting, and also abdominal cramps. In all cases, the individuals responded promptly to conservative treatment with antihistamine and occasionally adrenalin. Only in the one case of anaphylaxis was hospitalization necessary, and the Volunteer responded readily to adrenalin and steroid therapy. The reaction followed the first inoculation.

It would seem that a reaction rate of 6 or 7 per 1,000 individuals immunized is not an undue risk in light of the benefit the program provides. The Volunteers, because of the wide dispersion and the logistic problems involved, are not routinely checked for a positive response to vaccination. Rather, at the time of potential exposure to rabies, the individual is given the standard full course of prophylactic immunizations with duck embryo vaccine. It would seem that the rapid anamnesis and the higher titer give significant added protection, particularly in those individuals who fail to report the potential exposure until a week or more after the event has occurred. It also generally obviates the necessity for using anti-serum and its attendant hazard of sensitization and serum sickness.

In one study in the Philippines on antibody response following immunization, 20 Volunteers were bled 1 month after the last inoculation, and of this group, 18 of 20 demonstrated significant neutralizing antibody titers—with a response of 1:20 or greater to 15 MLD_{50}.

It appears that the present experience demonstrates the feasibility of the widespread use of duck embryo vaccine for pre-exposure immuno-prophylaxis against rabies. As other rabies vaccines with an even lower reaction rate are introduced, it would seem entirely feasible for large population groups to be immunized prior to exposure. This could provide significant protection to particular developing countries which have high mortality rates from rabies.

SCREWWORMS

US Dept of Agriculture Press Release, Washington, D.C., Oct 8, 1968.

Screwworm infestations are increasing in Texas and an epidemic is expected to become worse before cold weather begins to take its toll of these pests.

By early October, the screwworm laboratory at Mission, Texas, had identified over 4,000 cases from Texas, 89 from California, 279 from Arizona and 60 from New Mexico. This Texas peak is ahead of the 1963, the second worst year for screwworms, although, frequency of cases is below the 1962 level when over 50,000 cases were confirmed in the laboratory. Weather—mild, moist—provided an excellent climate for screwworm development, as well as good grazing in areas that ordinarily do not support livestock. The presence of more livestock and more untreated wounds compounded the problem. The screwworm plant at Mission, Texas, has been operating at top capacity and sterile flies are being released at close to 200 million a week in an attempt to keep up with the wild screwworm fly population.

Because of the tremendous success of the eradication program during the past few years, many ranchers now practice year-around calving which they could not do prior to the screwworm eradication program. The ranchers have also stopped looking for screwworms and treating wounds, precautionary measures which once were carried out routinely. Laboratory figures show that 1 out of every 4 cases of screwworms result from man-made wounds such as branding, dehorning, and shearing. Ranchers should resume searching for screwworms and examine their animals, collect suspected screwworm larvae and send them to the laboratory, treat wounds and spray cattle to kill screwworms.

HEPATITIS

USDHEW PHS NCDC Hepatitis Surv Rep No. 29, p 1–2, Sept 30, 1968.

During 31 Dec 1967–30 March 1968 of the hepatitis epidemiologic year, 11,707 cases of viral hepatitis were reported in the United States, for an attack rate of 5.9 cases per 100,000 population. This represents an increase of 5% over the winter quarter of the previous year.

When serum hepatitis cases are considered apart from total viral hepatitis cases, serum hepatitis cases increased 100% in the United States in the winter quarter 1967–68, compared with the corresponding quarter of 1966–67. Largest increase in reported cases of serum hepatitis occurred in the *Pacific Division.*

During 31 March–29 June 1968, 12,226 cases of viral hepatitis were reported, an incidence of 6.2 cases per 100,000 population. This is a 22% increase over the rate of 5.1 of the 1966–67 spring quarter. This is the third time since 1952 that the spring quarter incidence was higher than that of the preceding winter quarter. Serum hepatitis cases continued to increase, with the *Pacific Division* accounting for the bulk of this increase.

The overall trend for the United States during the last 3 epidemiologic years has been characterized by a continued rise in reported incidence of viral hepatitis. Most geographic divisions reflect this overall increase, but with considerable variation among the individual states.

The viral hepatitis surveillance program in the United States has been reviewed and revised. A 3-stage uniform surveillance system is now in operation. Each state can participate at that stage commensurate with its available resources.

Three unrelated outbreaks of infectious hepatitis are reported. Two episodes represent common source outbreaks, affecting school children predominantly. Source in one was a contaminated water supply, the other represents the first reported instance of hepatitis related to ingestion of contaminated bakery products. The third report deals with hepatitis at institutions for the mentally retarded.

A large person-to-person outbreak in Santa Lucia, Uruguay, occurred: The epidemiology of infectious hepatitis in this outbreak is similar to the United States experience. Children under 15 accounted for 65% of total number of cases. Attack rates were highest in the 5–9 and 10–14 age group.

Two reports of subhuman primate-associated hepatitis are presented in the report. Although young newly imported chimpanzees accounted for the bulk of previously reported episodes, one of the 2 outbreaks could not be associated with contact with this particular primate species.

(The figure may be seen in the original article.)

RABIES IN MAN AND ANIMALS IN THE UNITED STATES 1946–1965

NCDC Veterinary Public Health Notes of Feb 1968, p 2.

In 1946, the Public Health Service established a national rabies control program in its newly formed Communicable Disease Center, Atlanta, Georgia. As a part of this program, epidemiologic data on human and animal rabies have been collected from state health departments and other agencies that are responsible for rabies control within the various states.

The Nov 1967 issue of Public Health Reports presents a review of the epidemiology of rabies for the 20-years 1946–65.

During this period, the incidence of dog rabies in the U.S. declined markedly, with a concomitant decline in the number of persons who died of rabies. In 1946 there were 8,384 laboratory-confirmed cases of rabies in dogs, but in 1965 there were only 412. Thus dogs accounted for 75% of all cases of animal rabies in 1946, but for only 9% in 1965. Factors responsible for this decline included widespread immunization, stricter enforcement of stray-dog control, more extensive dissemination of public health information, and better pet care generally. The decline is even more significant in light of the increased number of owned dogs. In 1946, there were about 12 million dogs in the U.S.; in 1956 there were more than 25 million. After 1956, there

was a downward trend in the dog population to an estimated 22.9 million in 1965, still a substantial increase over the 1946 population.

From 1946 through 1965 there was a marked increase in cases of rabies in wildlife, principally in skunks, foxes, bats, and raccoons. Wildlife species are now responsible for half the cases reported in man.

Skunks and foxes accounted for the majority of cases in wildlife species.

Bats and raccoons are 2 other important species in the wildlife rabies picture in the U.S. Since rabies in insectivorous bats was first recognized in Florida in 1953, rabies virus has been isolated from bats in all states except Alaska, Hawaii, and Rhode Island. In 1965, 484 cases of bat rabies were reported. Raccoon rabies has been reported from widespread areas of the U.S. and cases have occurred primarily in the southeastern U.S. In 1965, 77 of the 99 cases of raccoon rabies reported in the U.S. occurred in Georgia and Florida.

From 1946 through 1965, 236 human rabies deaths were reported. There was a general decline in incidence of rabies in man, from 33 cases in 1946 to 1 each for the years 1963 and 1964, and 2 cases in 1965. Of 236 persons with rabies, 165 (70%) were males and 71 (30%) were females. The preponderance of cases in males reflects the fact that men and boys spend more time outdoors in activities that are more likely to bring them into contact with rabid animals.

There is evidence that postexposure immunoprophylactic therapy prevents some cases of rabies in man, particularly in persons for whom longer incubation periods would have been expected.

MYCOPLASMA PNEUMONIAE—ATLANTA, GEORGIA

USDHEW PHS NCDC Morb & Mort Wkly Rep 17(45):413–414, Nov 9, 1968.

Between 23 Sept and 16 Oct 1968, 27 cases of *Mycoplasma pneumoniae* occurred at a university in Atlanta, Georgia, among the members and pledges of one fraternity; 9 persons were hospitalized with clinical pneumonia, 4 were treated as outpatients, and 14 others reported illness on questionnaires distributed to the fraternity. Symptoms for the cases included malaise, fever, myalgia, severe headache, dizziness, coryza, sore throat, and non-productive cough. Physical findings of the hospitalized students included temperature of 102° to 104°F., erythema of the mucous membranes with occasional pharyngeal exudate, posterior cervical lymphadenopathy, and fine, localized rales; 4 students developed otitis media. White blood cell counts were within the normal range, but atypical lymphocytes were present on some peripheral blood smears. Duration of illness was about 8 days for about ½ of the cases. Similar illnesses occurred in 5 social acquaintances of 5 members and in the father and brother of another member. The laboratory partner of a non-ill fraternity member developed clinical primary atypical pneumonia on 30 Oct.

On 21 Oct., serum was collected from 55 members and pledges. Complement fixation and indirect hemagglutination geometric mean titers against *M. pneumoniae* on sera from 18 non-ill members were 1:13 and 1:28, respectively, and on sera from 18 convalescent students 1:129 and 1:142, respectively. Complement fixation titers on these same sera showed no rises against influenza A and B, parainfluenza 1, 2, and 3, adenoviruses, and psittacosis. Cultures of throat washings are in progress.

The epidemic curve suggested a common source of exposure for the outbreak. The only period when members and pledges shared a common environment prior to the outbreak was 18 Sept when all were present for pledge initiation and a catered dinner at a local cafeteria. Other common exposures which may account for later cases occurred on 28 Sept and 6 and 8 Oct.

HUMAN RABIES—ELK CITY, KANSAS

USDHEW PHS NCDC Morb & Mort Wkly Rep 17(42):389–390, Oct 19, 1968.

On 10 Oct 1968, a 13-year-old boy from Elk City, Kansas, died after a 63-day illness that has been diagnosed as rabies. His initial symptoms on 7 Aug were malaise, anorexia, nausea, and vomiting. Over the next 10 days he developed fever, confusion, hallucinations, numbness, paresthesias, and paresis of the right hand and arm. On 17 Aug, the boy experienced increased confusion and marked respiratory distress. That same day during his transfer to a hospital in Wichita, he suffered cardio-respiratory arrest, but was resuscitated after experiencing anoxic seizures. The next few days, he suffered several other respiratory arrests. He became comatose and had flaccid quadriplegia which lasted during the remainder of his illness. Throughout his hospitalization, but especially during the last 6 weeks, he had excessive salivation and respiratory tract secretions. He died following cardio-respiratory failure.

The patient had no known history of exposure to rabies, and clinical impression during his illness was encephalitis of unknown etiology. Routine hematologic and chemical tests were within normal limits; cerebrospinal fluid revealed a count of 87 white cells with 90% lymphocytes and a protein of 74 mg%. Stool cultures were negative for polio and other enteroviruses. Serologic tests were negative for Western equine, California, and St. Louis encephalitis and for mumps, lymphochorio-meningitis, poliomyelitis, psittacosis, and Rocky Mountain spotted fever. Rabies neutralizing antibody showed a rise in titer from 1:5 on serum drawn 17 Aug to 1:50 on serum drawn 6 Sept. These results were confirmed by indirect fluorescent antibody and complement-fixation tests. Fluorescent antibody staining for rabies antigen and mouse inoculation studies of the patient's brain following autopsy were positive, confirming the diagnosis of rabies.

Epidemiologic investigation in Elk City revealed a unique ecological opportunity for the development of human rabies. The town of 525 people in a rural area of southeastern Kansas has an animal population of at least 150 dogs, 150 cats, and an unknown number of stray animals. Both the human and animal populations are in close contact with a large skunk population in which rabies has been found. Immunization level in the domestic animals against rabies is less than 10%. The patient had a paper route, covering the entire town. He was bitten and nipped by many animals several times per week since acquiring the paper route in Jan 1968. Because of the lack of known exposure to a rabid animal, the boy received no antirabies therapy.

The following recommendations were made by local and state authorities in Kansas: (1) Vaccination of all dogs and cats against rabies; (2) Elimination of all stray animals; (3) A systematic reduction of the wild skunk population.

Editorial Note: This case of human rabies is the first acquired in the United States in 2 years. In 1967, 2 human cases acquired their infections in Africa.

THE POTENTIALS OF FREEZE DRYING

William Flieg, Jr., Freeze Dry Products, Inc., Evansville, Ind., J Milk Food Technology 31(8):251–252, Aug 1968.

Two directions of growth seem very promising and a third way would utilize the industry's potentials to the fullest.

The first two paths of growth are in the areas of institutional convenience feeding and industrial ingredients. Freeze-dried food offers large institutional feeders quickly prepared food that handle and store easily as well as assuring uniform quality, flavor and texture each time they are prepared. Dinner entrees, soups, salads and breakfast items are available to the mass feeder now and are doing very well.

The military is an extensive user of freeze-dried foods. Freeze-dried pouch packed meals for long range patrols (food packet, long patrol) are now replacing C-rations. The quality and acceptance has been so good that many soldiers are sending the packets home for their families to try.

Industrial ingredients refer to freeze-dried foods which are incorporated with other food products before they are sold to the end user. These ingredients afford the processor a quality dehydrated component that will enhance the final product and is generally easier to store and handle. Freeze-dried chives for dairy products, fruits with cereals, and meats, fishes and poultry for soups and casseroles are some examples.

Before discussing the industry's third area of growth potential, a brief explanation is given of the process for a fuller understanding of what freeze-dried foods have to offer.

It is well known that at sea level water boils at 212°. At Pike's Peak, the boiling temperature is less because there is less pressure. And, if the pressure is reduced, the boiling point soon drops to where it is equal to the freezing point of water. At this point, and lower, all water must exist in the form of ice. But, there is a boiling point at this pressure that causes the ice to change to a vapor of ice crystals without going through the liquid state—a process called cublimation.

The resulting water vapor is collected on refrigerated coils until the product is dry to less than 2% moisture. With proper packaging in a nitrogen atmosphere, and the low moisture content, the final product has a long shelf life.

Because the water leaves the product as a vapor the cell structure is not disturbed and there is no loss of color, flavor, or nutritional values. Also, the vapor leaves so gently that there is no surface hardening or any other objectionable property commonly associated with dehydrated foods. Thus, when water is replaced, the rehydrated product is virtually identical to the original in flavor, texture and appearance.

Thus, the third area of growth potential of freeze-drying offers completely new food products to the market place as well as increasing the availability of foods to new markets. A number of companies of freeze dryers are exploiting this potential by close cooperation with the food industry.

A perishable item as cottage cheese is being sold to Americans living overseas by a meat packing company. They are selling on the average of 7,200 pounds a month and that is in addition to the three million pounds this company sold to the military last year.

Freeze-dried ice cream enrobed in chocolate or other coverings is being used as a candy center. It's crunchy with the definite flavor of ice cream. Freeze-dried ice cream in cereal was also attempted as was the same product in an instant milk shake.

Horseradish kept losing its flavor, even while in a sauce. Now it is freeze dried, milled, and able to be put on the table and dispensed like salt. It releases its flavor when it comes in contact with any moist product.

Freeze drying obviously is not the only way, but it is an area to be investigated because of the potential it holds.

PUBLIC HEALTH—PART I

R. W. Emerson, MD 12(9):121–131, Sept 1968.

In the annals of mankind there are few tales more dramatic than the long arduous struggle to make common cause against disease and death. The outcome has sometimes proved more decisive than war in determining the rise and fall of empires, more important than politics in fixing the course of civilization.

Public health measures have been handed down from above by prophets and kings; they have been thrust up from below by reformers and revolutionaries. The movement has had its heroes who risked death for discovery, its intellectual giants who solved great riddles of existence, its visionaries who dreamed of new miracles and made some of them come true.

Today public health is a healing force in a double sense: peace and order elude a troubled world, but where health problems are concerned divided and quarreling nations work together for the general good.

Ancient. Early civilizations incorporated public health measures into religious codes; priestly sanctions were often invoked to enforce highly practical decrees. Among Hebrews the taboo on pork was a safeguard against trichinosis; it served also to protect the camp against the fly-breeding filth of the hog pen. A biblical passage warned Hebrews about pig-keeping: "Jehovah will smite thee with consumption and fever, with inflammation and with fiery heart."

About waste Deuteronomy advised: "Thou shall have a place without the camp wither thou shalt go forth abroad, and thou shalt have a paddle among thy weapons, and it shall be when thou wilt ease thyself abroad, thou shalt dig therewith and shalt turn back and cover that which cometh from thee."

Quarantine regulations were set forth in Leviticus: "All the days wherein the plague shall be in him, he shall be defiled; he is unclean; he shall dwell alone; without the camp shall his habitation be." Another verse specified a day of ritual cleansing for anyone who touched an infected person or his effects; for the sufferer himself 7 days of cleansing was prescribed.

Assyrian and Babylonian tribes adopted the fly as a symbol of Nergal, the god of disease and death. Through fear of flies they developed elaborate sanitation systems; towns were equipped with drains, sewers, stone privies; vultures were turned loose to cleanse battlefields and the dead were buried in deep trenches.

The Greeks introduced the rational concept, dealing with disease in terms of natural causes. Hippocrates stressed preventive medicine, urged physicians to study the etiology of illness. He coined the terms endemic and epidemic to distinguish between basic conditions, and he noted the importance of such contributing factors as climate, soil, water, mode of life, nutrition.

Philosopher and biologist Empedocles of Agrigentum (504–443 BC) is cited by Diogenes as a pioneer in practical environmental control. He reportedly turned 2 rivers into a marsh, draining stagnant waters to relieve a Sicilian epidemic that was probably malarial.

Public health engineering progressed steadily in Grecian culture, from Troy's ingenious water supply system to magnificent bathing facilities in the great era of Knossos on Crete. Greek cities designated officials called *astynomi* to supervise water supply, sewage and drainage.

The Romans contributed to public health their talents for massive construction and efficient organization. The empire's citizens became the best bathed people in all antiquity; more than a 1,000 public baths were supplied by 14 aqueducts totaling 1,300 miles in length; theoretically the daily per capita consumption was 130 gallons of fresh spring water.

Public health administration was advanced by the emperor Augustus; in 33 BC he established a water board to supervise supply sources and appointed the minister Agrippa as *edile* of the baths; the duties of the office included cleansing, policing, the maintenance of heating apparatus. Ediles later assumed responsibility for street sanitation, inspection of food markets and other public health functions.

Clinical services were inaugurated in Rome in the second century. Municipal physicians (*archiatri*) were employed to treat the poor; salaried physicians were retained also by the imperial court, the gladitorial schools and the baths. Infirmaries called *valetudinaria* were established for slaves, later became available to free citizens. The provinces offered clinics and convalescent homes operated by public funds. A military system maintained a series of army hospitals at strategic posts.

Medieval. In 542 bubonic plague erupted in Egypt and spread swiftly to engulf the known world.

The pandemic lasted 50 to 60 years, took some 100 million lives. Famine followed pestilence as farmers fled their fields, and commerce was strangled. One historian declared that the outbreak "depopulated towns, turned the country into a desert and made habitation of men to become the haunts of wild beasts."

Through the chaotic centuries in Europe the public health tradition was kept alive in the East. Byzantine emperors maintained the services developed in Rome, passed many of the ideas on to Islamic nations; Arabian rulers became noted especially as founders of public hospitals.

The famous Caliph Harun-al-Rashid established a hospital in 9th century Baghdad as part of his program to make that a scientific mecca for the Middle East. A century later another Baghdad hospital became the training center for an important medical school. At Cairo a 13th century hospital provided separate wards for fever patients, the wounded, and those with eye diseases, also special rooms for women. Islamic rulers founded at least 34 major public hospitals in medieval times.

Most monasteries maintained one or two rooms for the sick, with a pharmacy and perhaps a herbal garden. More elaborate facilities developed as some religious orders devoted themselves exclusively to healing. The Holy Ghost hospital was founded at Montpellier in 1145, became the model for similar hospitals established all over Europe by the order of the Holy Ghost.

Born of the Crusades was a paramedical group, the Knights of the Order of the Hospital of St. John of Jerusalem, known also as the Hospitallers. Beginning with a church infirmary at Jerusalem they expanded in the 12th century to a 2,000-bed hospital which offered the most advanced care of the period. Sick pilgrims to the Holy Land were provided with individual beds instead of being crowded together on dirty pallets; attendants were employed to wash the patients, change the linen and assist in feeding; the diet included fresh meat at least three times a week.

Municipal health services emerged slowly in medieval Europe: the initial stress was on sanitary measures enforced by elected officials. Milan in the 14th century had 6 overseers in charge of street cleaning and refuse disposal. At Amiens in the 15th century 2 officials were assigned to supervise the fish market, 2 for the retail sale of meat, 2 others for the baking and sale of bread, still others to inspect grocers and apothecaries. In some cities inspection duties were assumed by the guilds.

Paris introduced paved streets as a sanitary measure about 1185. In another major innovation Augsburg sponsored the first known municipal slaughterhouse in 1276; most other communities at the time allowed indiscriminate slaughtering within the city limits.

A few cities regulated pollution of streams by tanners and dyers: Douay passed such an ordinance in 1271, Augsburg in 1453, Rome in 1468. Many cities provided wells and fountains for drinking water; in Germany and Italy the fountains were often beautifully designed and became motifs for distinctive city emblems.

Despite sanitation efforts most medieval communities were overwhelmed by filth. Only the wealthy could afford latrines which emptied into cesspools; among the ordinary people a dozen families often shared an outhouse. Hogs were kept in city pens, ordure littered the streets, water conduits were frequently mere hollow logs which swarmed with vermin. Municipal cleansing lagged so far behind needs that Moslem visitors complained of Europe as a place of "infidel smells."

Medieval public diseases that can be identified include bubonic plague, leprosy, smallpox, diphtheria, measles, influenza, ergotism, tuberculosis, scabies, erysipelas, anthrax, trachoma, the sweating sickness. A particular scourge was leprosy, probably acquired from the Middle East. It began to spread through Europe in the 6th century, reached pandemic proportions in the 13th and 14th centuries; attempts to contain it brought the first concerted efforts for isolation of infected persons. The Council of Lyons

restricted free association of lepers with healthy persons in 583; other increasingly stringent regulations were imposed by clerical and civic authorities through the centuries that followed.

Lepers were banned from markets, inns and other places of public assembly, were often reduced to the life of wandering mendicants. They were required to wear distinctive clothing, had to use bells, rattles or clappers to warn wayfarers of their approach. In some communities their exclusion was symbolized by a mock funeral; the sufferer was clad in a shroud, the mass for the dead was said for him and he was led from the city accompanied by wailing relatives and friends.

An early public health measure was the creation of leper houses to shelter victims; by the beginning of the 13th century there were some 2,000 such establishments in France, about 19,000 in Europe.

The medical disaster of the era was a fearful outbreak of bubonic plague. Called the Black Death the pandemic began in China, sped along trade routes to India and Egypt, reached Europe in 1348. It killed an estimated 25 million people in Europe alone (about 25% of the population) and probably as many more in Asia. Death tolls included 60,000 people in Florence, 50,000 in Paris, 70,000 in London; in some areas of Germany 90% of the population was swept away.

In Italy municipal authorities took measures for controlling water supplies and disposing of infected clothing. Venice became the first city to forbid entry to travelers who might be infected; later the republic Ragusa established an automatic quarantine (*quarantenaria*) in which sailors and cargo from plague areas were detained on an island for 40 days.

KNOW YOUR WORLD

Did You Know?

That alcohol and home accidents in persons 15–64, account for 8,300 fatalities and more than 8.5 million nonfatal injuries annually?

A study of home accidents indicates that alcohol plays an important role among young adults and the middle-aged.[1]

That an outbreak of food poisoning due to *Clostridium perfringens* occurred on 14 Sept 1968 in New York City, among members of a company following a banquet dinner at a hotel?

Of 1,800 members participating more than 900 (or 50%) became ill with headache, nausea, abdominal cramps, and diarrhea. Incubation mean period was 15 hours with a range from 2–26 hours, and the illness lasted 12–24 hours. Roast beef was found to be contaminated.[2]

That smallpox declined in most parts of the world during first half of 1968?

WHO reports that up to 11 July 1968, 36,382 cases had been reported or 25,000 less than during the same period in 1967. West and Central Africa, show the most marked decrease, with a total number of 3,289 or a drop from 6,148 cases. Only Togo showed a significant increase during this period.

Eradication programs began in most of the countries concerned in 1967, and by the end of March 1968 over 32 million of 115 million people living in these countries had been vaccinated. Increasingly vigorous efforts have been made to detect and investigate cases and combat outbreaks. Despite improvement in reporting in 1968, this year's figures are the lowest in recorded history.[3]

The first successful typhus vaccines were prepared in Poland by the Polish Doctor Wiegl?

Having great difficulty finding suitable medium upon which to grow the tiny organisms which caused the disease, the only medium he knew was in the intestine of the living louse; his experiments, therefore, were carried out by inoculating the living organism of typhus into the intestines of lice. He trained his workers in the delicate task of inserting very fine glass pipettes into the anal orifice of the tiny insect. As can be imagined this was very tedious and difficult business and did not produce very large amounts of vaccine. It required about 150 lice to provide sufficient vaccine for 1 person. This meant that extensive louse farms had to be kept going and they could only be fed on human volunteers immune from the disease. Wiegl had about 200 of them who had recovered from typhus fever and so were immune. A great advance was made, however, when it was found in America that the organism could be grown on live chicken embryos. The vac-

cine used at the present time is prepared from organisms which have been cultivated by inoculation of fertile eggs. [4]

That *Papio papio* baboon is the first animal other than man found to have epilepsy that occurs naturally and appears to be a species characteristic?

This was discovered accidently in 1965 by researchers who were studying the effects of drugs on cats, primates and man. On routine testing, 4 of the 10 West African baboons went into convulsions. This was the first time that normal animals had responded with convulsions to flashing light. Additional *P. papios* tested showed a close similarity in brain wave patterns, sleep records, and reactions to drugs between the baboons and epileptic patients. [5]

That flare-up of malaria may assume epidemic proportions in India if more effective antimalaria measures, especially DDT spraying are not intensified?

The people of India have supposedly "almost lost immunity against malaria parasite during the last 10 years." Two top-ranking Indian officials are seeking assistance from the United States and the World Health Organization; both of which have helped India to fight malaria previously. [6]

That a total of 12,578 cases of skin disease were reviewed in Vancouver, British Columbia, Canada?

The eczema group comprised 39.2% of the total with contact dermatitis the most common single disorder. Next in frequency were tumors—8.5%; acne—7.3%; viral infections—6.8%; bacterial infections—5.7%; psoriasis—4.7% fungal infections —4.3%; alopecia—2.3%; parasitic infestation—2.1%; and pruritus—1.9%. [7]

That up to 31 August 1968, 327 cases of poliomyelitis were confirmed in Venezuela with poliovirus Type I as the most prevalent agent?

A nationwide campaign was begun on 29 September 1968, Sabin monovalent Type I oral vaccine to be administered to 700,000 unvaccinated children under 3 years of age in all States and Federal Territories of Venezuela. [8]

That in South Vietnam, immunizations against smallpox, cholera and plague have risen from 4.1 million in 1966 to some 9 million in the first 4 months of 1968?

That rice production in South Vietnam was up a half million tons in 1967–68 over 1966, with 50,000 acres now planted with the new high-yield rice seed? [9]

That the total number of reported tetanus cases in 1965 was 300 with 181 fatalities; 235 in 1966 and 233 in 1967 with mortality not yet available?

One-third of all wounds associated with tetanus cases in 1965–1966 were puncture wounds, with lacerations being second (25% of total) most commonly associated wounds, according to the NCDC, Atlanta, survey. [10]

That a "mass juvenile sweep" was organized in 1964 against yaws control in St. Lucia, West Indian island?

A yaws eradication program was instituted in St. Lucia in 1957, and in 1963, of the notified cases, 77% were children under age 15. Of 3,442 children examined, 294 had active yaws and were administered intramuscularly benzathine penicillin on an age basis to a maximum of 1,200,000 units. The rest of the children were given a smaller dose of benzathine penicillin. In the next 2 years, only 3 notifications of yaws from this district have occurred. [11]

That a 57-year-old dentist returned to Florida on 29 October 1968 from safari in Rhodesia and Botswana (formerly Bechuanaland) with an acute illness, African sleeping sickness?

The illness was characterized by chills, fever, lethargy, malaise, axillary lymphadenopathy and a skin lesion on the right forearm. While on safari, he had been bitten by numerous tsetse flies and had developed symptoms shortly before returning to Florida, where he was hospitalized on 1 November. Blood smears revealed numerous trypanosomes. No malaria parasites were seen. A lumbar puncture revealed 1 lymphocyte and a protein of 22 mg%. Suramin (available from the Parasitic Disease Drug Service, NCDC, Atlanta), the drug of choice for early hemolymphatic Rhodesian sleeping sickness was begun on 3 November, and was continued for 3 weeks, the recommended period of administration. [12]

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EDITOR'S SECTION

PRESCRIPTION DRUGS

A 339-page study on the use of prescription drugs by the elderly—and on their ability to pay for them —was released by the Task Force on Prescription Drugs of the Department of Health, Education, and Welfare.

Entitled *The Drug Users,* the publication is the first of a series of detailed, documented background papers prepared by the Task Force, which was created to undertake a comprehensive study of the problems of including the cost of out-of-hospital prescription drugs under Medicare.

Other background papers now in preparation are devoted to drug manufacturing, drug distribution, drug prescribing, and drug quality.

Preliminary findings and recommendations were presented in two interim reports by the Task Force earlier this year.

Dr. Philip R. Lee, Assistant Secretary for Health and Scientific Affairs and chairman of the Task Force said:

"These studies are, of course, directly related to the use of prescription drugs by elderly Americans, but we believe that the findings and the recommendations based upon them will help to improve the quality of health care for all Americans."

The Drug Users is devoted to an analysis of the financial resources of the elderly, their health needs, their health expenditures, and their patterns of drug use.

As part of the study, investigations were conducted to determine—

—Which drugs, by brand or generic name, are most frequently dispensed for the elderly.

—Which diseases or conditions account for the greatest drug use.

—Which drugs are most frequently involved in long-term maintenance therapy.

To find answers to such questions, the Task Force compiled a Master Drug List consisting of the 409 drugs most frequently used by the elderly. They involved about 175 million out-of-hospital precriptions, costing $682 million at the retail level, and accounted for 88 percent of all prescription drug costs for the elderly in 1966—the most recent year for which complete data were available.

The 10 most frequently dispensed drugs included the following: tolbutamide, for the treatment of diabetes; chlordiazepoxide, a tranquilizer; chlorothiazide, a diuretic used in the treatment of kidney and heart disease; indomethacin, used in the treatment of arthritis and similar ailments; hydrochlorothiazide, a diuretic; digoxin, used in the treatment of heart disease; glutethimide, a sedative; aspirin, caffeine, phenacetin and propoxyphene, used to relieve pain; phenobarbital, a sedative; and diazepam, a tranquilizer.

During the year, these 10 drugs accounted for about 20 percent of the total cost of drugs on the Master Drug List.

Of these 10, the Task Force report showed, eight were still under patent and no chemical equivalents were available from multiple sources under generic name. One drug—phenobarbital—was dispensed commonly under its generic name. Only one-digoxin —was widely prescribed under its brand name although a less expensive counterpart was available under a generic name.

Of the 409 drugs, the largest group represented products used for the treatment of heart disease and hypertension. These were followed in turn by drugs used for arthritis and rheumatism, and those prescribed for mental and nervous conditions.

Of these 409 drugs, it was also found that—

—290 were still under patent, with no generic name products available from competing suppliers;

—30 were available and actually dispensed under generic name;

—22 were available under generic name, but not at any appreciable saving over brand name products; and

—only 67 could have been obtained from more than one supplier, at a cost distinctly lower than that of the brand name product actually dispensed.

If these 67 had been dispensed as low-cost generic name products, the savings at the retail level —providing the same mark-up were set by the pharmacist—were estimated to be about $41.5 million, or 27.7 percent on the 67 products involved.

Additional savings could have been achieved, Dr. Lee said, if the use of generic name products had been incorporated with the use of formularies and other methods currently utilized in a variety of governmental and private drug programs.

The Task Force study also focussed on various price indices which seem to demonstrate that, on the one hand, drug prices are decreasing, and on the other, that they are increasing.

"According to the Consumer Price Index of the Bureau of Labor Statistics," the report said, "these

prices have been falling steadily since about 1959. According to three other yardsticks, however, they have been rising steadily since that date."

The apparent discrepancy, the report noted, is due to the fact that these various indices are used to measure different things.

"The Consumer Price Index is designed to measure prices of a 'market basket' of a variety of consumer products over a period of time. In the case of drugs, it appears to demonstrate simply that the average of the prices of those products selected in the 'market basket'—14 were included in 1967—has been decreasing."

But, the report noted, the drugs selected for the "market basket" do not necessarily reflect the nature of drugs which comprise those most widely used by the public in general and by the elderly in particular. The CPI index is so designed that it does not reflect the impact of new and costly products which may be introduced on the market and replace older and less expensive drugs.

"The CPI is thus not relevant to the changes which have been occurring in the average price of all prescriptions purchased by patients," it was stated.

The irrelevancy is indicated by changes shown by three independent indices—the Lilly Digest Index, the National Prescription Audit, and the American Druggist Index—which demonstrate that while the price of certain selected drugs may have been decreasing, the average price of all prescriptions has been increasing at the rate of about 2 percent per year during the past decade.—USDHEW, Office of the Secretary, Washington, D.C.

SYMPOSIUM ON COMMON PROBLEMS IN NAVY PHARMACOLOGY

Thirty-three Navy Pharmacists attended a one-day symposium at the National Naval Medical Center, Bethesda, Maryland on 25 October 1968, the day following the Federal Services Pharmacy Seminar at the Sheraton-Park Hotel, Washington, D.C. CDR Katherine Keating chaired the discussion program of mutual interest items and common problems in pharmacy in the Navy. The interest generated during this meeting was such that it is proposed that an annual symposium follow the Military Surgeon's Annual Convention and Federal Services Pharmacy Seminar in the Washington Area.—Medicine Branch, BuMed.

CONFERENCE TRAVEL FOR MEDICAL OFFICERS

All Medical Officers should be familiar with the provisions of SECNAV INSTRUCTION 4651.15A which provides guidance for attendance at professional meetings, conferences, symposia, and seminars.

Historically, this instruction results from a memorandum issued 17 April 1967, by the Deputy Secretary of Defense which stated that "it is desirable that all Medical Corps Officers stationed in the United States be offered an opportunity to attend at least one professional medical conference per year on a temporary additional duty basis and that those stationed outside the United States should have the same opportunity, to the extent that their location and military operations permit." The prompting force behind the issuance of the DOD Memorandum was a recommendation in the Report of the Retention Task Force which stated that the inability to continue professional growth is a strong determining factor in the young medical officer's decision to leave the Naval Service.

Funds in support of the program outlined in SECNAV INSTRUCTION 4651.15A were included in Expense Operating Budgets of Naval Hospitals and other activities under the financial support of BUMED. Commands (less BUMED command activities holding Expense Operating Budgets under the appropriation Operations, Navy) are authorized to cite accounting data for centrally held funds. Requests for attendance at civilian sponsored meetings, conferences, symposia, short courses and seminars should be made on the NAVEXOS 12000/2 which may be approved by Commanding Officers of Naval Hospitals or by the first echelon in the chain of command having approval authority in the case of medical officers who are attached to other than BUMED Command Activities.

In order to keep a complete history of medical officers' participation in continuing education, it is essential that copies of all Temporary Additional Duty orders be forwarded to BUMED and BUPERS in accordance with the procedures outlined in SECNAV INSTRUCTION 4651.15A.—Training Branch, BuMed.

SUPPORT FOR TRAINING PROGRAMS

Purpose of Announcement

The purpose of this announcement is to outline opportunities for training support available under the programs of the National Center for Prevention and Control of Alcoholism. The Center was established in 1966 to stimulate research on the control and prevention of alcoholism; to accelerate communication and application of research findings to treatment and

preventive activities; to encourage the development of training programs and to modify public attitudes toward alcoholism by publicizing scientific knowledge through an expanded program of education.

The Manpower and Training Section of the Center hopes to expand training opportunities for professional and nonprofessional personnel in the approaches, methods and potential techniques for treatment and prevention of alcoholism and the rehabilitation of alcoholics and their families. The Center also encourages the recruitment of students into the future manpower pool of persons knowledgeable about alcoholism from a research standpoint. To increase training opportunities in the field of alcoholism, the Manpower and Training Section, through the grant program, will support training in a wide variety of disciplines, as well as conferences and demonstration programs, which would exemplify novel training situations to serve as future model programs.

Priorities

The Manpower and Training Section has established the following as priority activities:

1. Teaching about alcohol-related problems to persons enrolled in training institutions for the helping professions, such as medical schools (including internships and residency training), schools of social work, schools of nursing, schools of public health and psychology departments. Such institutions will be encouraged to develop new materials, integrate and improve teaching about alcohol problems in their curricula. Concomitant with this approach is the need to train current faculty of these institutions and to evaluate all new training programs.

2. Updating and upgrading knowledge and skills in relation to alcoholism of current practitioners in the mental health field. Such programs could occur in a variety of settings such as hospitals, community mental health centers, mental health clinics and others. They would probably be mainly of an inservice and continuing education nature.

3. Intensive training of a cadre of professionals, from a variety of disciplines, who plan to make a substantial professional commitment in the field of alcoholism in relation to teaching, research, treatment or administration.

4. Training of the volunteer, the nonprofessional, and other professionals (such as the teacher, the clergyman, the policeman, the lawyer) whose jobs may bring them into contact with alcohol-related problems.

How and When to Apply

Closing dates for filing applications are June 1, October 1, and February 1. For further information write to:

Dr. George Retholtz
Chief, Manpower and Training Section
National Center for Prevention and Control of Alcoholism
National Institute of Mental Health
5454 Wisconsin Avenue
Chevy Chase, Maryland 20203

—USDHEW, National Institute of Mental Health, Chevy Chase, Md.

JOURNAL OF TRAUMA

The 7 June 1968 issue of the Navy Medical News Letter, Vol 51, No. 11, contained an article by CDR C. E. Brodine, MC, USN, entitled "National Academy of Science, National Research Council Conference on Pulmonary Effects of Non-Thoracic Trauma, Selected Comments." Proceedings of the entire conference have been published in the September 1968 special issue of *The Journal of Trauma,* Volume 8, No. 5. It is to be noted that, although single copies of *The Journal of Trauma* cost $4.00 each, copies of this particular conference issue may be obtained for $3.00 per copy from The Williams & Wilkins Company, 428 East Preston Street, Baltimore, Maryland 21202.

DENTAL OFFICERS PARTICIPATE IN ANNUAL AMERICAN DENTAL ASSOCIATION MEETING

RADM E. C. Raffetto, DC USN, Assistant Chief of the Bureau of Medicine and Surgery (Dentistry) and Chief, Dental Division, attended the Annual Meeting of the American Dental Association, Miami Beach, Florida, October 27–31, 1968, as Navy Delegate. Other active duty dental officers who participated in the professional program of the meeting were:

CAPT Philip J. Boyne—"Treatment of Avulsed Teeth and Alveolar Process Fractures"

CAPT Perry Alexander—"Correlation of Roentgenographic and Clinical Aspects of Periodontal Disease"

CAPT William H. Lieser—"Prognathic Splint Construction"

CDR James D. Enoch—"Service With Pin-Retained Amalgam Restorations"

LCDR Robert E. Cassidy—"The Chilled Silver Cone as a Root Canal Filling Material"

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